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(54) Title: NOVEL PYRIMIDINE COMPOUNDS USEFUL IN TREATING CYTOKINE MEDIATED DISEASES

(57) Abstract

This invention relates to the novel amino substituted pyrimidine compounds of Formulas (I), (II) and (III), and pharmaceutical compositions comprising a compound of these Formulas and a pharmaceutically acceptable diluent or carrier. This invention also relates to a method of inhibiting CSBP kinase and cytokines mediated by this kinase, for the treatment of cytokine mediated diseases, in mammals, by administration of a compound of Formula (I), (II) or (III).

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5 NOVEL PYRIMIDINE COMPOUNDS USEFUL IN TREATING
CYTOKINE MEDIATED DISEASES

FIELD OF THE INVENTION

This invention relates to a novel group of pyrimidine compounds, processes for the preparation thereof, the use thereof in treating cytokine mediated diseases and pharmaceutical compositions for use in such therapy.

BACKGROUND OF THE INVENTION:

15 Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are biological substances produced by a variety of cells, such as monocytes or macrophages. IL-1 has been demonstrated to mediate a variety of biological activities thought to be important in immunoregulation and other physiological conditions such as inflammation [See, e.g., Dinarello et al., *Rev. Infect. Disease*, 6, 51 (1984)]. The myriad of known biological activities of IL-1 include the activation of T helper cells, induction of fever, stimulation of prostaglandin or collagenase production, neutrophil chemotaxis, induction of acute phase proteins and the suppression of plasma iron levels.

There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, and acute synovitis. Recent evidence also links IL-1 activity to diabetes and pancreatic β cells.

30 Dinarello, J. Clinical Immunology, 5 (5), 287-297 (1985), reviews the biological activities which have been attributed to IL-1. It should be noted that some of these effects have been described by others as indirect effects of IL-1.

Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic

shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, 5 cachexia secondary to infection or malignancy, cachexia, secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been 10 identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1, HIV-2 infect T lymphocytes after T Cell activation and such virus protein expression and/or replication is mediated 15 or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Monokines, specifically TNF, are implicated in activated T-cell mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, 20 interference with monokine activity such as by inhibition of monokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, 25 such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T-cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg *et al.*, The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, (1989)]. Monokines, such as TNF, have been shown to activate HIV replication in 30 monocytes and/or macrophages [See Poli, *et al.*, Proc. Natl. Acad. Sci., 87:782-784 (1990)], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T-cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalia virus (CMV), influenza virus, and the herpes virus for similar 35 reasons as those noted.

Interleukin -8 (IL-8) is a chemotactic factor first identified and characterized in 1987. IL-8 is produced by several cell types including mononuclear cells, fibroblasts, endothelial cells, and keratinocytes. Its production from endothelial cells is induced by IL-1, TNF, or lipopolysaccharide (LPS). Human IL-8 has been shown to act on

5 Mouse, Guinea Pig, Rat, and Rabbit Neutrophils. Many different names have been applied to IL-8, such as neutrophil attractant/activation protein-1 (NAP-1), monocyte derived neutrophil chemotactic factor (MDNCF), neutrophil activating factor (NAF), and T-cell lymphocyte chemotactic factor.

IL-8 stimulates a number of functions in vitro. It has been shown to have

10 chemoattractant properties for neutrophils, T-lymphocytes, and basophils. In addition it induces histamine release from basophils from both normal and atopic individuals as well as lysozymal enzyme release and respiratory burst from neutrophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without de novo protein synthesis, this may contribute to increased

15 adhesion of the neutrophils to vascular endothelial cells. Many diseases are characterized by massive neutrophil infiltration. Conditions associated with an increased in IL-8 production (which is responsible for chemotaxis of neutrophils into the inflammatory site) would benefit by compounds which are suppressive of IL-8 production.

20 IL-1 and TNF affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

25 There remains a need for treatment, in this field, for compounds which are cytokine suppressive anti-inflammatory drugs, i.e. compounds which are capable of inhibiting cytokines, such as IL-1, IL-6, IL-8 and TNF.

SUMMARY OF THE INVENTION

30 This invention relates to the novel compounds of Formulas (I), (II), and (III) and pharmaceutical compositions comprising a compound of Formula (I), (II), or (III), respectively, and a pharmaceutically acceptable diluent or carrier.

This invention also relates to a method of inhibiting cytokines and the treatment of a cytokine mediated disease, in a mammal in need thereof, which

comprises administering to said mammal an effective amount of a compound of Formula (I), (II), or (III).

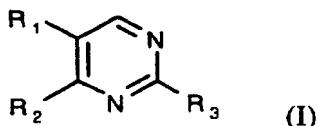
This invention more specifically relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I), (II), or (III).

This invention more specifically relates to a method of inhibiting the production of IL-8 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I), (II), or (III).

This invention more specifically relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of Formula (I), (II), or (III).

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention are represented by the structure having the formula:



wherein:

R₁ is 4-pyridyl, 4-pyrimidinyl, 4-quinazolinyl, 4-quinolyl, or 6-isoquinoliny, which rings are optionally substituted with one or two substituents, each of which is independently selected from Y, NHR_a, optionally substituted C₁₋₄ alkyl, halogen, hydroxyl, optionally substituted C₁₋₄ alkoxy, optionally substituted C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, or N(R₁₀)C(O)R_b;

Y is X₁-R_a;

X₁ is oxygen or sulfur;

R_a is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclC₁₋₆ alkyl, heteroaryl, heteroarylC₁₋₆alkyl, wherein each of these moieties may be optionally substituted;

R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocycl, or heterocyclC₁₋₄ alkyl, wherein each of these moieties may be optionally substituted;

R₂ is an optionally substituted aryl or optionally substituted heteroaryl group, provided that both R₁ and R₂ are not the same heteroaryl group;

and when R₂ is an optionally substituted aryl ring, the ring is substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano, -C(Z)NR₁₃R₁₄, -C(Z)OR₂₃, -(CR₁₀R₂₀)_nCOR₃₆, -SR₁₅, -SOR₁₅, -OR₃₆, 5 halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, -ZC(Z)R₃₆, -NR₁₀C(Z)R₂₃, or -(CR₁₀R₂₀)_nNR₁₀R₂₀ and which, for other positions of substitution, is halo, cyano, -C(Z)NR₁₆R₂₆, -C(Z)OR₈, -(CR₁₀R₂₀)_nCOR₈, -S(O)_mR₈, -OR₈, halo-10 substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, -(CR₁₀R₂₀)_nNR₁₀C(Z)R₈, -NHS(O)_mR₇, -NHS(O)_mNR₁₃R₁₄, -NR₇S(O)_mR₇, -NR₇S(O)_{m'}NR₁₃R₁₄ wherein m' is 1 or 2, -ZC(Z)R₈ or -(CR₁₀R₂₀)_nNR₁₆R₂₆;

and when R₂ is an optionally substituted heteroaryl group, the substituent groups include one or two substituents each of which is independently selected from C₁₋₄ alkyl, halo, C₁₋₄ alkoxy, C₁₋₄ alkylthio, NR₁₀R₂₀, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂;

15 m is 0 or an integer of 1 or 2;

n is 0 or an integer of 1 or 2;

R₃ is hydrogen, NR₅R₆, NHS(O)₂R₇, NR₁₀C(Z)R₈, NR₁₀C(Z)NR₅R₆, NR₁₀C(=NR₁₁)NR₅R₆, or NR₁₀C(Z)OR₁₀; wherein the alkyl, aryl, arylalkyl, 20 heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl moieties of R₇, and R₈ may be optionally substituted;

R₅ and R₆ are each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 25 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉;

Z is oxygen or sulfur;

R₇ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroarylkyl;

30 R₈ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylkyl;

R₉ is hydrogen, -C(Z)R₈ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₇, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;

R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₆ alkyl;

35 R₁₁ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;

R₁₂ is R₁₀ or C(Z)-C₁₋₄ alkyl, optionally substituted aryl, optionally substituted arylC₁₋₄ alkyl, or S(O)₂R₇;

R₁₃ and R₁₄ is each independently selected from hydrogen or C₁₋₄ alkyl or R₁₃ and R₁₄ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₂₂;

5 R₁₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₁₃R₁₄, provided that the moiety -SR₁₅ is not -SNR₁₃R₁₄ and the moiety -S(O)R₁₅ is not -SOH;

R₁₆ and R₂₆ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 10 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂ ;

R₂₂ is R₁₀ or C(Z)-C₁₋₄ alkyl;

15 R₂₃ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;

R₃₆ is hydrogen or R₂₃;

or a pharmaceutically acceptable salt thereof.

Suitable heteroaryl moieties for R₁ and R₂ are 4-pyridyl, 4-pyrimidinyl, 4-quinazolinyl, 4-quinolyl, or 6-isoquinoliny, 1-imidazolyl, 1-benzimidazolyl and 20 thiophene. Preferably the heteroaryl ring is a 4-pyridyl, 4-pyrimidinyl, 4-quinazolinyl, 4-quinolyl, or 6-isoquinoliny ring. More preferably the heteroaryl group is a 4-pyridyl, or 4-pyrimidinyl ring. Preferably, the 4-pyridyl group is substituted in the 2-position and the 4-pyrimidinyl group is substituted at the 2- or 4- position.

Each of these heteroaryl rings may be optionally substituted with one or two 25 substituents, each of which is independently selected from Y, NHR_a, optionally substituted C₁₋₄ alkyl, halogen, hydroxyl, optionally substituted C₁₋₄ alkoxy, optionally substituted C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, or N(R₁₀)C(O)R_b.

Y is suitably Y is X₁-R_a ; and X₁ is oxygen or sulfur, preferably 30 oxygen. R_a is suitably a C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclC₁₋₆ alkyl, heteroaryl, heteroarylC₁₋₆alkyl group, wherein each of these moieties may be optionally substituted.

R_b is suitably hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocycl, or heterocyclC₁₋₄ alkyl, wherein each 35 of these moieties may be optionally substituted as defined herein.

When the R₁ substituent is Y, and R_a is aryl, it is preferably phenyl or naphthyl.

When R_a is aryl alkyl, it is preferably benzyl or naphtylmethyl. When R_a is heterocyclic or heterocyclic alkyl moiety, the heterocyclic portion is preferably pyrrolindinyl, piperidine, morpholino, tetrahydropyran, tetrahydrothiopyranyl, tetrahydrothiopyran-sulfinyl, tetrahydrothio-pyransulfonyl, pyrrolindinyl, indole, or piperonyl. It is noted that the heterocyclic rings herein may contain unsaturation, such as in a tryptamine ring.

The R_a aryl, heterocyclic and heteroaryl rings may be optionally substituted one or more times independently with halogen; C₁-4 alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted alkyl, such as CF₃; hydroxy; hydroxy substituted C₁-4 alkyl; C₁-4 alkoxy, such as methoxy or ethoxy; S(O)_malkyl and S(O)_m aryl (wherein m is 0, 1, or 2); C(O)OR₁₁, such as C(O)C₁-4 alkyl or C(O)OH moieties; C(O)R₁₁; -OC(O)R_c; O-(CH₂)_s-O-, such as in a ketal or dioxoalkylene bridge; amino; mono- and di-C₁-6 alkylsubstituted amino; -N(R₁₀)C(O)R_b; -C(O)NR₁₀R₂₀; cyano, nitro, or an N-heterocyclic ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₅; aryl, such as phenyl; an optionally substituted arylalkyl, such as benzyl or phenethyl; aryloxy, such as phenoxy; or arylalkyloxy such as benzyloxy. Wherein R_c is optionally substituted C₁-6 alkyl, C₃-7 cycloalkyl, aryl, arylC₁-4 alkyl, heteroaryl, heteroarylC₁-4alkyl, heterocyclyl, or heterocyclylC₁-4 alkyl moieties.

Preferably, the R_a groups include benzyl, halosubstituted benzyl, naphtylmethyl, phenyl, halosubstituted phenyl, aminocarbonylphenyl, alkylphenyl, cyanophenyl, alkylthiophenyl, hydroxyphenyl, alkoxyphenyl, morpholinopropyl, piperonyl, piperidin-4-yl, alkyl substituted piperidine, such as 1-methyl piperidine, or 2,2,6,6-tetramethylpiperidin-4-yl.

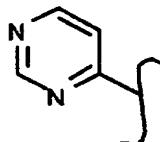
Preferably, when the substituent is NHR_a then R_a is aryl, such as phenyl or naphthyl; arylalkyl, such as benzyl, or naphtylmethyl; halosubstituted arylalkyl, halosubstituted aryl; heterocyclic alkyl, such as morpholinopropyl; hydroxy alkyl; alkyl-1-piperidine-carboxylate; heterocyclic, such as piperonyl, or piperidin-4-yl; alkyl substituted heterocyclic, such as alkyl substituted piperidine; halosubstituted heterocyclic; or aryl substituted heterocyclic.

Preferably, when the R₁ substituent is an optionally substituted C₁-4 alkoxy or C₁-4 alkylthio, the alkyl chain may be substituted by halogen, such as fluorine, chlorine, bromine or iodine; hydroxy, such as hydroxyethoxy; C₁-10 alkoxy, such as a methoxymethoxy, S(O)_m alkyl, wherein m is 0, 1 or 2; amino, mono & di-substituted amino, such as in the NR₇R₁₇ group, i.e. tert-butylaminoethoxy; or where the R₇R₁₇ may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom

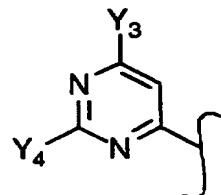
selected from O/N/S; C1-10 alkyl, cycloalkyl, or cycloalkyl alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; or halosubstituted C1-10 alkyl, such as CF₃.

Preferred substituents for the heteroaryl ring R₁ is C1-4 alkyl, NH₂ or 5 monosubstituted C1-4 alkyl amino, i.e. wherein both R₁₀ and R₂₀ are preferably hydrogen or one of R₁₀ and R₂₀ is hydrogen and the other is a C1-4 alkyl. Preferably, when the substituent is a C1-4 alkyl group it is methyl, and when the substituent is the mono-substituted amino, it is preferably -NH(CH₃).

For the purposes herein when the R₁ is a 4-pyrimidinyl moiety the "core" 10 pyrimidinyl is referred to as having the formula:



When the R₁ (or R₂) 4-pyrimidinyl moiety is substituted it is preferably substituted in at least one of the following position by the moiety Y₃ and Y₄ which are referred to herein in greater detail as optional substituents on the heteroaryl rings 15 R₁ and R₂.



As the nomenclature will change when either Y₃ or Y₄ is substituted, for the purposes herein when Y₄ but not Y₃ is the substituted position it is referred to as the 2- position. When Y₃ but not Y₄ is the substituted position it is referred to as the 4- position and the point of attachment of the pyrimidinyl ring is not the 6-position. 20

Suitable aryl groups for R₂ include optionally substituted phenyl, naphth-1-yl or naphth-2-yl. Preferably R₂ is an optionally substituted phenyl. These aryl rings may be optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, -naphth-1-yl or 5-naphth-2-yl 25 substituent, is halo, cyano, -C(Z)NR₁₃R₁₄, -C(Z)OR₂₃, -(CR₁₀R₂₀)_n COR₃₆, -SR₁₅, -SOR₁₅, -OR₃₆, halo-substituted-C1-4 alkyl, C1-4 alkyl, -ZC(Z)R₃₆, -NR₁₀C(Z)R₂₃, or -(CR₁₀R₂₀)_n NR₁₀R₂₀ and which, for other positions of substitution, is halo, cyano, -C(Z)NR₁₆R₂₆, -C(Z)OR₈, -(CR₁₀R₂₀)_n COR₈,

-S(O)_mR₈, -OR₈, halo-substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, -(CR₁₀R₂₀)_nNR₁₀C(Z)R₈, -NHS(O)_mR₇, -NHS(O)_mNR₁₃R₁₄, -NR₇S(O)_mR₇, -NR₇S(O)_{m'}NR₁₃R₁₄ wherein m' is 1 or 2, -ZC(Z)R₈ or -(CR₁₀R₂₀)_nNR₁₆R₂₆.

Preferred substitutions for R₂ when it is a 4-phenyl, 4-naphth-1-yl or 5-

5 naphth-2-yl moiety are one or two substituents each independently selected from halogen, -SR₁₅, -SOR₁₅, -OR₃₆, or -(CR₁₀R₂₀)_nNR₁₀R₂₀, and for other positions of substitution on these rings preferred substitution is halogen, -S(O)_mR₈, -OR₈, (CR₁₀R₂₀)_nNR₁₆R₂₆, -(CR₁₀R₂₀)_nNR₁₀C(Z)R₈ and -NR₇S(O)_mR₇. More preferred substituents for the 4-position in phenyl and naphth-1-yl and on the

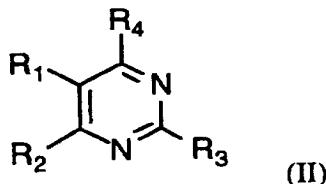
10 5-position in naphth-2-yl include halogen, especially fluoro and chloro, and -SR₁₅ and S(O)R₁₅ wherein R₁₅ is preferably a C₁₋₂ alkyl, more preferably methyl; of which fluoro is especially preferred. Preferred substituents for the 3-position in phenyl and naphth-1-yl include: halogen, especially chloro; -OR₈, especially C₁₋₄ alkoxy; amino; -NR₁₀C(Z)R₈, especially -NHCO(C₁₋₁₀alkyl); and -NR₁₀S(O)_mR₁₁, especially

15 NHSO₂(C₁₋₁₀ alkyl). Preferably, the aryl group is an unsubstituted or substituted phenyl moiety. More preferably, it is phenyl or phenyl substituted at the 4-position with fluoro and/or substituted at the 3-position with fluoro, chloro, C₁₋₄ alkoxy, methanesulfonamido or acetamido.

Suitably, R₃ is -hydrogen, NR₅R₆, NHS(O)₂R₇, NR₁₀C(Z)R₈,
20 NR₁₀C(Z)NR₅R₆, NR₁₀C(=NR₁₁)NR₅R₆, or NR₁₀C(Z)OR₁₀; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl moieties of R₅, R₆, R₇, R₈, R₁₀, and R₁₁ may be optionally substituted as herein defined.

25 In a preferred subgenus of compounds of formula (I), R₁ is 4-pyridyl, 2-alkyl-4-pyridyl, 2-NR₁₀R₂₀-4-pyridyl, 4-pyrimidinyl, 2-alkyl-4-pyrimidinyl, 2-NR₁₀R₂₀-4-pyrimidinyl, or 4-quinolyl; R₂ is an optionally substituted phenyl group. More preferably R₂ is phenyl or phenyl substituted by fluoro, chloro, C₁₋₄ alkoxy, S(O)_mC₁₋₄ alkyl, methanesulfonamido or acetamido.

Another aspect of the present invention are the novel compounds of Formula (II):



5 wherein:

R₁ is 4-pyridyl, 4-pyrimidinyl, 4-quinazolinyl, 4-quinolyl, or 6-isoquinolinyl, which rings are optionally substituted with one or two substituents, each of which is independently selected from Y, NHR_a, optionally substituted C₁₋₄ alkyl, halogen, hydroxyl, optionally substituted C₁₋₄ alkoxy, optionally substituted C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, or N(R₁₀)C(O)R_b;

Y is X₁-R_a;

X₁ is oxygen or sulfur;

R_a is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl,

15 heteroaryl, heteroarylC₁₋₆alkyl, wherein each of these moieties may be optionally substituted;

R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclic, or heterocyclylC₁₋₄ alkyl, wherein each of these moieties may be optionally substituted;

20 R₂ is an optionally substituted aryl or optionally substituted heteroaryl group, provided that both R₁ and R₂ are not the same heteroaryl group; wherein when one R₂ is an optionally substituted aryl ring, the ring is substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano, -C(Z)NR₁₃R₁₄,

25 -C(Z)OR₂₃, -(CR₁₀R₂₀)_n COR₃₆, -SR₁₅, -S(O)R₁₅, -OR₃₆, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, -ZC(Z)R₃₆, -NR₁₀C(Z)R₂₃, or -(CR₁₀R₂₀)_n NR₁₀R₂₀ and which, for other positions of substitution, is halo, cyano, -C(Z)NR₁₆R₂₆, -C(Z)OR₈, -(CR₁₀R₂₀)_n COR₈, -S(O)_mR₈, -OR₈, halo-substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, -(CR₁₀R₂₀)_nNR₁₀C(Z)R₈, -NHS(O)_mR₇, -NHS(O)_mNR₁₃R₁₄,

30 -NR₇S(O)_mR₇, -NR₇S(O)_m'NR₁₃R₁₄ wherein m' is 1 or 2, -ZC(Z)R₈ or -(CR₁₀R₂₀)_n NR₁₆R₂₆; and when R₂ is an optionally substituted heteroaryl group, the substituent groups include one or two substituents each of which is

independently selected from C₁-4 alkyl, halo, C₁-4 alkoxy, C₁-4 alkylthio, NR₁₀R₂₀, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂;

5 m is 0 or an integer of 1 or 2;
n is 0 or an integer of 1 or 2;
R₃ and R₄ are independently NR₅R₆, NHS(O)₂R₇, NR₁₀C(Z)R₈, NR₁₀C(Z)NR₅R₆, NR₁₀C(=NR₁₁)NR₅R₆, or NR₁₀C(Z)OR₁₀;
R₅ and R₆ are each independently selected from hydrogen or optionally substituted

10 C₁-4 alkyl, optionally substituted aryl or optionally substituted aryl-C₁-4 alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉;
Z is oxygen or sulfur;

15 R₇ is C₁-10 alkyl, C₃-7 cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁-10alkyl, heteroaryl or heteroarylalkyl; wherein all of these moieties may be optionally substituted;
R₈ is hydrogen, C₁-10 alkyl, C₃-7 cycloalkyl, heterocyclyl, heterocyclyl C₁-10alkyl, aryl, arylC₁-10 alkyl, heteroaryl or heteroarylC₁-10 alkyl; wherein all of these

20 moieties may be optionally substituted;
R₉ is hydrogen, -C(Z)R₈ or optionally substituted C₁-10 alkyl, S(O)₂R₇, optionally substituted aryl or optionally substituted aryl-C₁-4 alkyl;
R₁₀ and R₂₀ is each independently selected from hydrogen or C₁-4 alkyl;
R₁₁ is hydrogen, cyano, C₁-4 alkyl, C₃-7 cycloalkyl or aryl;

25 R₁₂ is R₁₀ or C(Z)-C₁-4 alkyl;
R₁₃ and R₁₄ is each independently selected from hydrogen or C₁-4 alkyl or R₁₃ and R₁₄ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₇;

30 R₁₅ is hydrogen, C₁-4 alkyl, C₂-4 alkenyl, C₂-4 alkynyl or NR₁₃R₁₄, provided that the moiety -SR₁₅ is not -SNR₁₃R₁₄ and the moiety -S(O)R₁₅ is not -SOH;
R₁₆ and R₂₆ is each independently selected from hydrogen or optionally substituted C₁-4 alkyl, optionally substituted aryl or optionally substituted aryl-C₁-4 alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to

7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9;

R17 is hydrogen of C(Z)-C1-4 alkyl;

R23 is C1-4 alkyl, halo-substituted-C1-4 alkyl, or C3-5 cycloalkyl;

5 R36 is hydrogen or R23;
or a pharmaceutically acceptable salt thereof.

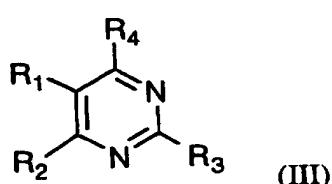
Suitable heteroaryl moieties for R1 and R2 in Formula (II) are those as defined above for Formula (I), as are the remaining substituent groups, but for the R3 and R4 variables defined below.

10 Suitably, R3 and R4 are NR5R6, NHS(O)2R7, NR10C(Z)R8, NR10C(Z)NR5R6, NR10C(=NR11)NR5R6, or NR10C(Z)OR10; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl moieties of R7, R8, R10, R11 may be optionally substituted as defined herein. More preferably, R3 and R4 are NR5R6 and R5 and R6 are independently hydrogen or C1-4 alkyl.

15 In a preferred subgenus of compounds of formula (II), R1 is 4-pyridyl, 2-alkyl-4-pyridyl, 2-NR10R20-4-pyridyl, 4-pyrimidinyl, 2-alkyl-4-pyrimidinyl, 2-NR10R20-4-pyrimidinyl, or 4-quinolyl; R2 is an optionally substituted phenyl group. More preferably R2 is phenyl or phenyl substituted by fluoro, chloro, C1-4 alkoxy, S(O)mC1-4 alkyl, methanesulfonamido or acetamido.

20

In yet another embodiment of the present invention are the novel compounds of Formula (III):



wherein:

R1 is 4-pyridyl, 4-pyrimidinyl, 4-quinazolinyl, 4-quinolyl, or 6-isquinolinyl, which rings are optionally substituted with one or two substituents, each of which is independently selected from Y, NHRa, optionally substituted C1-4 alkyl, halogen, hydroxyl, optionally substituted C1-4 alkoxy, optionally substituted C1-4 alkylthio, C1-4 alkylsulfinyl, CH2OR12, amino, mono and di-C1-6 alkyl substituted amino, or N(R10)C(O)Rb;

30

Y is $X_1\text{-}R_a$;

X_1 is oxygen or sulfur;

R_a is C_{1-6} alkyl, aryl, aryl C_{1-6} alkyl, heterocyclic, heterocyclic C_{1-6} alkyl, heteroaryl, heteroaryl C_{1-6} alkyl, wherein each of these moieties may be

5 optionally substituted;

R_b is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, aryl C_{1-4} alkyl, heteroaryl, heteroaryl C_{1-4} alkyl, heterocyclic, or heterocyclic C_{1-4} alkyl, wherein each of these moieties may be optionally substituted;

R_2 is an optionally substituted aryl or optionally substituted heteroaryl group,

10 provided that both R_1 and R_2 are not the same heteroaryl group; wherein when one R_2 is an optionally substituted aryl ring, the ring is substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano, $-\text{C}(Z)\text{NR}_{13}\text{R}_{14}$, $-\text{C}(Z)\text{OR}_{23}$, $-(\text{CR}_{10}\text{R}_{20})_n\text{COR}_{36}$, $-\text{SR}_{15}$, $-\text{S}(\text{O})\text{R}_{15}$, $-\text{OR}_{36}$, halo-substituted- C_{1-4} alkyl, C_{1-4} alkyl, $-\text{ZC}(Z)\text{R}_{36}$, $-\text{NR}_{10}\text{C}(Z)\text{R}_{23}$, or $-(\text{CR}_{10}\text{R}_{20})_n\text{NR}_{10}\text{R}_{20}$ and which, for other positions of substitution, is halo, cyano, $-\text{C}(Z)\text{NR}_{16}\text{R}_{26}$, $-\text{C}(Z)\text{OR}_8$, $-(\text{CR}_{10}\text{R}_{20})_n\text{COR}_8$, $-\text{S}(\text{O})_m\text{R}_8$, $-\text{OR}_8$, halo-substituted- C_{1-4} alkyl, $-C_{1-4}$ alkyl, $-(\text{CR}_{10}\text{R}_{20})_n\text{NR}_{10}\text{C}(Z)\text{R}_8$, $-\text{NHS}(\text{O})_m\text{R}_7$, $-\text{NHS}(\text{O})_m\text{NR}_{13}\text{R}_{14}$, $-\text{NR}_7\text{S}(\text{O})_m\text{R}_7$, $-\text{NR}_7\text{S}(\text{O})_m\text{NR}_{13}\text{R}_{14}$, $-\text{ZC}(Z)\text{R}_8$ or $-(\text{CR}_{10}\text{R}_{20})_n\text{NR}_{16}\text{R}_{26}$;

15 and when R_2 is an optionally substituted heteroaryl group, the substituent groups include one or two substituents each of which is independently selected from C_{1-4} alkyl, halo, C_{1-4} alkoxy, C_{1-4} alkylthio, $\text{NR}_{10}\text{R}_{20}$, or an N-heterocyclic ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12} ;

20 and when R_2 is an optionally substituted heteroaryl group, the substituent groups include one or two substituents each of which is independently selected from C_{1-4} alkyl, halo, C_{1-4} alkoxy, C_{1-4} alkylthio, $\text{NR}_{10}\text{R}_{20}$, or an N-heterocyclic ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{12} ;

25 m is 0 or an integer of 1 or 2;

m' is an integer of 1 or 2;

m'' is an integer having a value of 1 to 10;

n is 0 or an integer of 1 or 2;

n' is 0 or an integer having a value of 1 to 10;

30 n'' is an integer having a value of 1 to 10

R_3 is hydrogen, C_{1-10} alkyl, halosubstituted C_{1-10} alkyl, $-(\text{CR}_{10}\text{R}_{20})_n\text{Q}\text{-}(Y_1)_t$, $-(\text{CR}_{10}\text{R}_{20})_n\text{(Y}_2\text{)}_p$, $-(\text{CR}_{10}\text{R}_{20})_n\text{(Y}_3\text{)}_p$, or $-(\text{CR}_{10}\text{R}_{20})_m\text{(Y}_4\text{)}_p$;

p is 0 or an integer of 1 or 2

t is an integer of 1, 2, or 3;

35 Q is an aryl or heteroaryl group;

Y₁ is independently selected from hydrogen, halogen, C₁-5 alkyl, halo-substituted C₁-5 alkyl, -(CR₁₀R₂₀)_{n'} (Y₂)_p, -(CR₁₀R₂₀)_{n''}(Y₃)_p, or -(CR₁₀R₂₀)_{m''} (Y₄)_p;

Y₂ is halogen, -OR₈, -S(O)_{m'}R₁₈, -SR₈, -S(O)_{m'}OR₈, -S(O)_{m'}NR₈R₉, or -O(CR₁₀R₂₀)_{n'}NR₈R₉, -ZC(O)R₈, or -OC(Z)NR₈R₉;

5 Y₃ is -NR₈R₉, -NR₁₀C(Z)R₈, -NR₁₀C(Z)NR₈R₉, -NR₁₀S(O)_{m'}R₁₈, -N(OR₂₁)C(Z)NR₈R₉, -N(OR₂₁)C(Z)R₈, -NR₁₀C(=NR₁₁)SR₁₈, -NR₁₀C(=NR₁₁)NR₈R₉, -NR₁₀C(=CR₁₄R₂₄)SR₁₈, -NR₁₀C(=C(R₂₄)₂)NR₈R₉, -NR₁₀C(O)C(O)NR₈R₉, -NR₁₀C(O)C(O)OR₁₀, -NR₁₀S(O)_{m'}CF₃, or -NR₁₀C(Z)OR₁₀;

10 Y₄ is -C(O)R₈, -CO₂R₈, -CO₂(CR₁₀R₂₀)_{m''} CONR₈R₉, -CN, -C(Z)NR₈R₉, -C(Z)NR₈OR₉, -C(=NOR₂₁)R₈, -C(=NR₁₉)NR₈R₉, -C(=NOR₁₉)NR₈R₉, -C(=NR₁₉)ZR₁₈, -NR₁₀S(O)_{m'}CF₃, or -NR₁₀C(Z)OR₁₀;

R₄ is hydrogen, NR₅R₆, NHS(O)₂R₇, NR₁₀C(Z)R₈, NR₁₀C(Z)NR₅R₆, NR₁₀C(=NR₁₁)NR₅R₆, or NR₁₀C(Z)OR₁₀; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl moieties of R₇, and R₈ may be optionally substituted;

15 R₅ and R₆ are each independently selected from hydrogen or optionally substituted C₁-4 alkyl, optionally substituted aryl or optionally substituted aryl-C₁-4 alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₇;

Z is oxygen or sulfur;

R₇ is C₁-10 alkyl, C₃-7 cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁-10alkyl, heteroaryl or heteroarylalkyl;

20 25 R₈ is hydrogen, C₁-10 alkyl, C₃-7 cycloalkyl, heterocyclyl, heterocyclyl C₁-10alkyl, aryl, arylC₁-10 alkyl, heteroaryl or heteroarylC₁-10 alkyl;

R₉ is hydrogen, C₁-10 alkyl, C₂-10 alkenyl, C₂-10 alkynyl, C₃-7 cycloalkyl, C₅-7 cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R₈ and R₉ may together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₇;

30 R₁₀ and R₂₀ is each independently selected from hydrogen or C₁-4 alkyl;

R₁₁ is hydrogen, cyano, C₁-4 alkyl, C₃-7 cycloalkyl or aryl;

R₁₂ is R₁₀ or C(Z)-C₁-4 alkyl;

R₁₃ and R₁₄ is each independently selected from hydrogen or C₁₋₄ alkyl or R₁₃ and R₁₄ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₂₂;

5 R₁₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₁₃R₁₄, provided that the moiety -SR₁₅ is not -SNR₁₃R₁₄ and the moiety -S(O)R₁₅ is not -SOH;

R₁₆ and R₂₆ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to

10 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₇;

R₁₇ is hydrogen, -C(Z)R₈ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₇, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;

R₁₈ is C₁₋₁₀ alkyl, halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

15 R₁₉ is hydrogen, C₁₋₁₀ alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R₂₁ is hydrogen, a pharmaceutically acceptable cation, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, aryl C₁₋₄ alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C₁₋₁₀ alkanoyl;

20 R₂₂ is R₁₀ or C(Z)-C₁₋₄ alkyl;

R₂₃ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;

R₂₄ is independently selected from hydrogen, alkyl, nitro or cyano;

R₃₆ is hydrogen or R₂₃;

25 or a pharmaceutically acceptable salt thereof.

Suitable heteroaryl moieties for R₁ and R₂ in Formula (III) are the same as defined above for Formula (I), as are the remaining substituent groups, but for R₃ and R₄ variables defined below.

30 Suitably, R₄ is NR₅R₆, NHS(O)₂R₇, NR₁₀C(Z)R₈, NR₁₀C(Z)NR₅R₆, NR₁₀C(=NR₁₁)NR₅R₆, or NR₁₀C(Z)OR₁₀; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl moieties of R₅, R₆, R₇, R₈, R₁₀, and R₁₁ may be optionally substituted as herein defined. More preferably R₄ is NR₅R₆ and R₅ and R₆ are hydrogen or C₁₋₄ alkyl.

Suitably, R₃ is hydrogen, C₁₋₁₀ alkyl, halosubstituted C₁₋₁₀ alkyl, -(CR₁₀R₂₀)_{n'}Q-(Y₁)_t, -(CR₁₀R₂₀)_{n'}(Y₂)_p, -(CR₁₀R₂₀)_{n''}(Y₃)_p, or -(CR₁₀R₂₀)_{m''}(Y₄)_p. Preferably when R₃ is -(CR₁₀R₂₀)_{n'}Q-(Y₁)_t then Q is aryl, and t is 1. Suitably R₃ is -(CR₁₀R₂₀)_{n''}(Y₃)_p.

5 Y₂ is suitably halogen, -OR₈, -S(O)_{m'}R₁₈, -SR₈, -S(O)_{m'}OR₈, -S(O)_mNR₈R₉, or -O(CR₁₀R₂₀)_nNR₈R₉, -ZC(O)R₈, or -OC(Z)NR₈R₉.
 Y₃ is suitably -NR₈R₉, -NR₁₀C(Z)R₈, -NR₁₀C(Z)NR₈R₉, -NR₁₀S(O)_mR₁₈, -N(OR₂₁)C(Z)NR₈R₉, -N(OR₂₁)C(Z)R₈, -NR₁₀C(=NR₁₁)SR₁₈, -NR₁₀C(=NR₁₁)NR₈R₉, -NR₁₀C(=CR₁₄R₂₄)SR₁₈, -NR₁₀C(=C(R₂₄)₂)NR₈R₉.

10 -NR₁₀C(O)C(O)NR₈R₉, -NR₁₀C(O)C(O)OR₁₀, -NR₁₀S(O)_mCF₃, or -NR₁₀C(Z)OR₁₀.
 Y₄ is suitably -C(O)R₈, -CO₂R₈, -CO₂(CR₁₀R₂₀)_{m''}CONR₈R₉, -CN, -C(Z)NR₈R₉, -C(Z)NR₈OR₉, -C(=NOR₂₁)R₈, -C(=NR₁₉)NR₈R₉, -C(=NOR₁₉)NR₈R₉, -C(=NR₁₉)ZR₁₈, -NR₁₀S(O)_mCF₃, or -NR₁₀C(Z)OR₁₀.

15 In all instances herein where there is an alkenyl or alkynyl moiety as a substituent group, the unsaturated linkage, i.e., the vinylene or acetylene linkage is preferably not directly attached to the nitrogen, oxygen or sulfur moieties, for instance in C(Z)NR₈OR₉, NR₁₀C(Z)NR₈R₉, or OR₈.

20 As used herein, for all formulas, "optionally substituted" unless specified, refers to such groups as halogen, halo C₁₋₆ alkyl, C₁₋₆ alkyl, hydroxyl, hydroxyl substituted C₁₋₆ alkyl, C₁₋₆ alkoxy, S(O)_m C₁₋₆ alkyl, amino, a mono & di C₁₋₆alkyl substituted amino, C₃₋₇ cycloalkyl, aryl or arylalkyl wherein the cycloalkyl and aryl moieties may be optionally substituted by halogen, hydroxyl, alkoxy, S(O)_m C₁₋₆ alkyl, amino, a mono & di- C₁₋₆alkyl substituted amino, C₁₋₆ alkyl, or halo C₁₋₆ alkyl.

30 Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of formula (I) may also be formed with a pharmaceutically acceptable

cation, for instance, if a substituent Y₁ in R₃ comprises a carboxy group. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

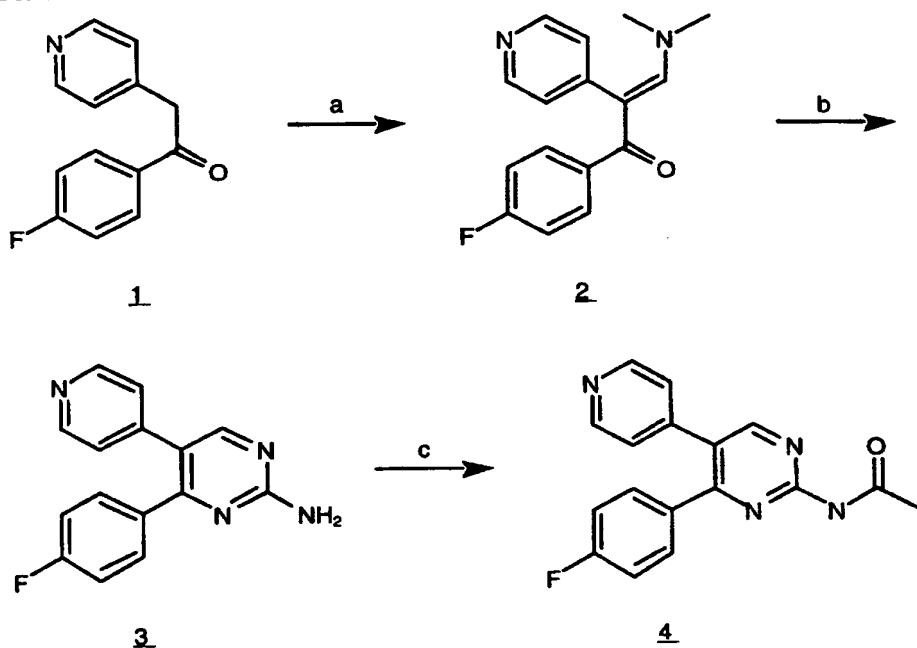
5 The following terms, as used herein, refer to:

- "halo" - all halogens, that is chloro, fluoro, bromo and iodo;
- "C₁₋₁₀alkyl" or "alkyl" - both straight and branched chain radicals of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and the like;
- The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 7 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy") - a 15 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, thiophene, quinoline, isoquinoline, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole;
- "heterocyclic" (on its own or in any combination, such as 20 "heterocyclalkyl") - a saturated or wholly or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, imidazolidine or pyrazolidine;
- The term "aralkyl" or "heteroarylalkyl" or "heterocyclalkyl" is used herein 25 to mean C₁₋₄ alkyl as defined above unless otherwise indicated
- "sulfinyl" - the oxide S(O) of the corresponding sulfide while the term "thio" refers to the sulfide.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

5 Compounds of Formula (I) may be readily prepared using procedures well known to those of skill in the art and may be prepared by analogous methods to those indicated herein below.

Scheme I



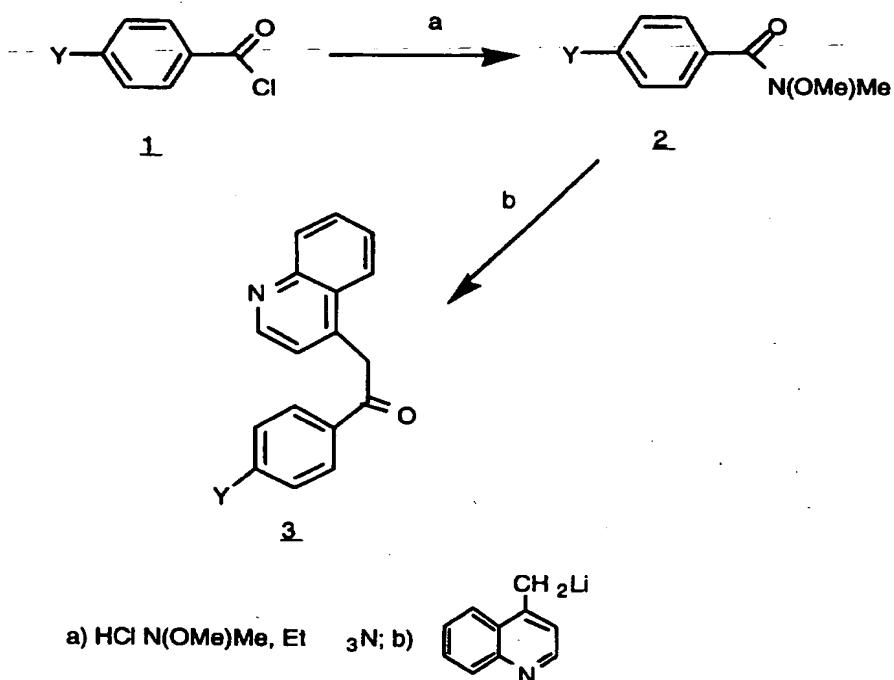
10 a) $(CH_3O)_2CHN(CH_3)_2$; b) $H_2NC(=NH)NH_2, HCl, NaOEt, EtOH$; c) Ac_2O

While the illustration in Schemes I and II are for the preparation of a particular compound of Formula (I) (i.e., Scheme I, R_1 =-pyridyl, R_2 =4-fluorophenyl and R_3 =acetamide), generalization of the synthesis to groups claimed as R_1 and R_2 and R_3 herein can be achieved by starting with the appropriate acetophenones, preparation of which are disclosed in PCT/US93/00674, notably Scheme I, whose disclosure is herein incorporated by reference. Conversion of the appropriate acetophenone to the corresponding enamine 2 is outlined in EP 0 531 901 A2 whose disclosure is incorporated by reference herein. Treatment of 2 with a guanidine, or a mono- or di-

alkyl guanidine, affords pyrimidine 3 where R₃ is equal to a primary, secondary or tertiary amino group, respectively. The desired guanidines are either commercially available or can be prepared by the procedure outlined in Oxley, P. et al., *J. Chem. Soc.*, (1951), 1252 whose disclosure is incorporated by reference herein. Pyrimidine 3 can be converted to additional compounds of Formula (I) wherein R₃ is the corresponding sulphonamide, amide, urea, guanidine or urethane by using techniques well known to those of skill in the art of the appropriate acylating agents, such as sulfonyl chlorides, acid chlorides, isocyanates, dicyanamides and chloroformates, respectively.

10

Scheme II

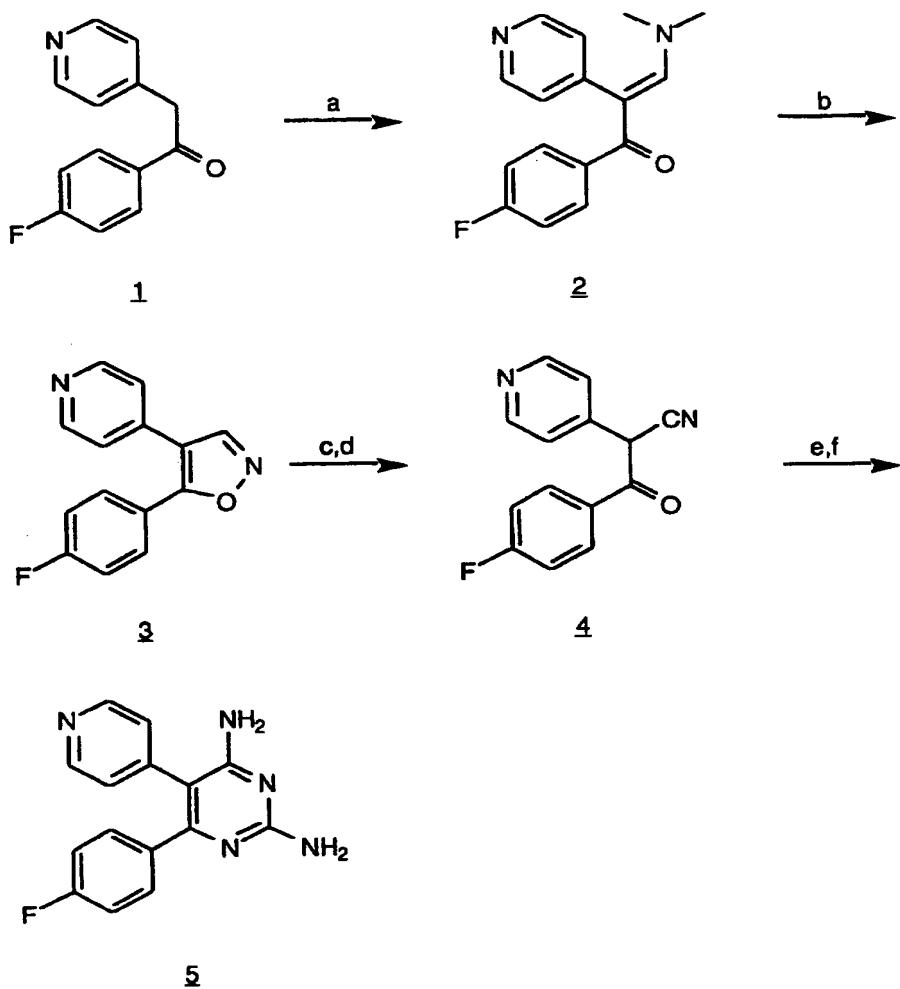


The appropriately substituted acetophenone, 3-Scheme-II, is prepared by adding 15 the anion of 4-methyl-quinoline (step b), which is prepared by treatment thereof with an alkyl lithium derivative, such as *n*-butyl lithium, to an N-alkyl-O-alkoxybenzamide. Suitably, the other R₁ moieties may be prepared in an analogous manner. Alternatively, the anion may be condensed with a benzaldehyde, to give an alcohol which is then oxidized to the ketone 3.

20

Compounds of Formula (II) are also pyrimidine derivatives which may be readily prepared using procedures well known to those of skill in the art and may be prepared by analogous methods to those indicated herein below.

Scheme III



5

a) $(CH_3O)_2CHN(CH_3)_2$; b) $H_2NOH \cdot HCl$; c) $NaOH$; d) HCl ; e) $TBDMSi_2O, CH_2Cl_2$;

f) $H_2NC(=NH)NH_2 \cdot HCl, EtOH$

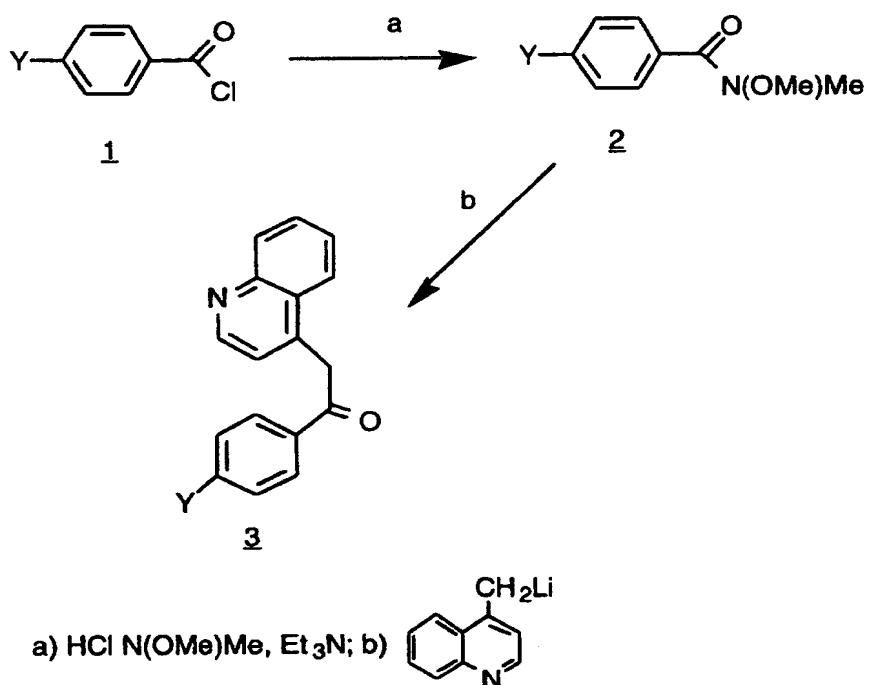
While the illustration in Schemes III and IV are for the preparation of a particular compound of Formula (II) (i.e., Scheme IV, R_1 =-pyridyl, R_2 =4-fluorophenyl, R_4 =amino and R_3 =hydrogen), generalization of the synthesis to groups

10 claimed as R_1 and R_2 and R_3 herein can be achieved by starting with the appropriate acetophenones, preparation of which are disclosed in PCT/US93/00674, notably

Scheme IV, whose disclosure is incorporated by reference herein. Conversion to the corresponding enamine 2, isoxazole 3 and propanenitrile 4 is outlined in EP 0 531 901 A2 whose disclosure is incorporated by reference herein. Conversion of propanenitrile 4 is facilitated by formation of an enol ether derivative (e.g., a silyl enol ether). Subsequent treatment with guanidine, or a mono- or dialkyl guanidine, affords pyrimidine 5 where R₃ is equal to a primary, secondary or tertiary amino group, respectively, and R₄ is NH₂. The desired substituted guanidines (resulting in R₃) are either commercially available, or can be prepared by the procedure outlined in Oxley, P. *et al.*, *J. Chem. Soc.*, (1951), 1252. The R₃ group of a pyrimidine 5 may if needed, be protected prior to derivatization, of the amino group (R₄) such as noted below. Alternatively, the R₃ moiety may also be de-protected and derivatized as well. Suitable derivitazation and protection techniques are well known by one of skill in the art. For instance, when R₃ is a dialkyl amine, R₄ can be converted to the corresponding sulphonamide, amide, urea, guanidine or urethane by using the appropriate acylating agents such as sulfonyl chlorides, acid chlorides, isocyanates, dicyanamides and chloroformates, respectively. When R₃ is a primary amine, R₃ and R₄ can be converted to the bis-sulphonamides, bisamides, bisureas, bisguanidines or bisurethanes by using the appropriate acylating agents such as those listed above, with appropriate separation techniques if need be.

20

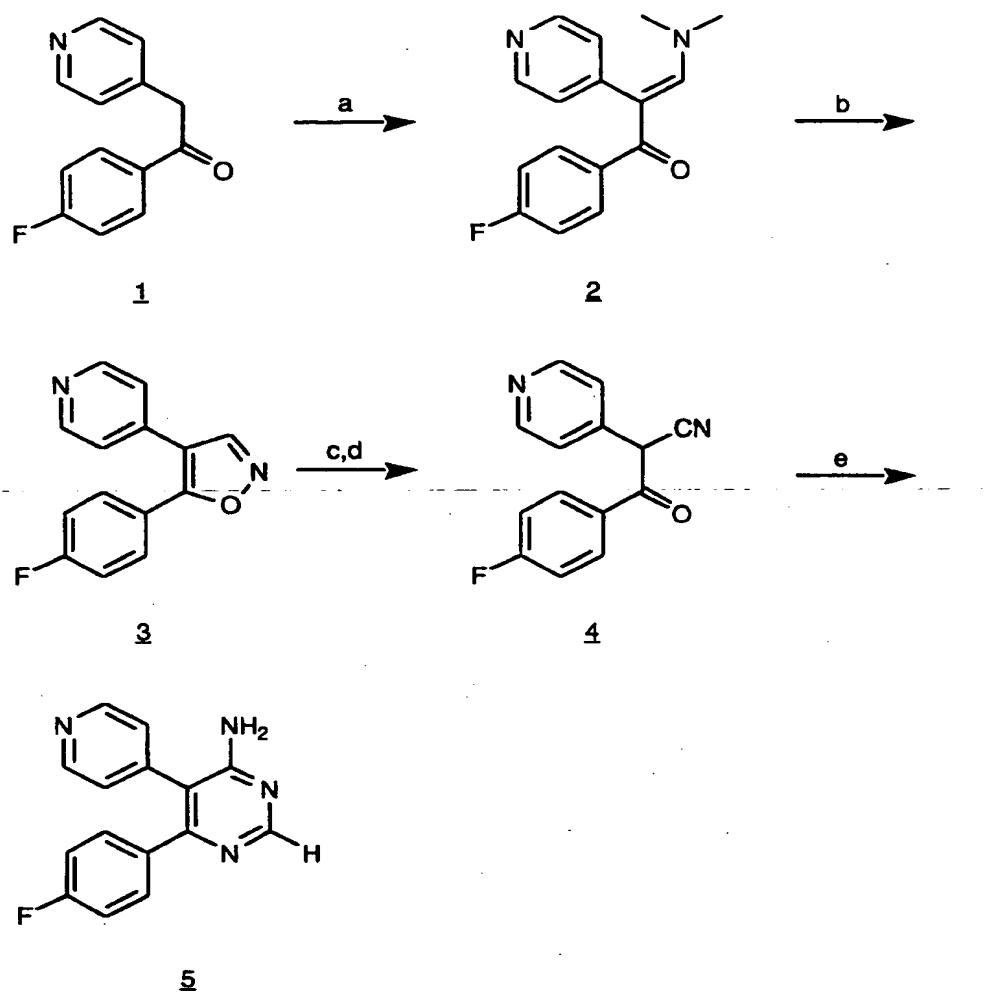
Scheme IV



The appropriately substituted acetophenone, 3 of scheme 4 is prepared by adding the anion of 4-methyl-quinoline (step b), which is prepared by treatment 5 thereof with an alkyl lithium derivative, such as *n*-butyl lithium, to an N-alkyl-O-alkoxybenzamide. Suitably, the other R₁ moieties may be prepared in an analogous manner. Alternatively, the anion may be condensed with a benzaldehyde, to give an alcohol which is then oxidised to the ketone 3.

Compounds of Formula (III) are pyrimidine derivatives which may be readily 10 prepared using procedures well known to those of skill in the art and may be prepared by analogous methods to those indicated below.

Scheme V

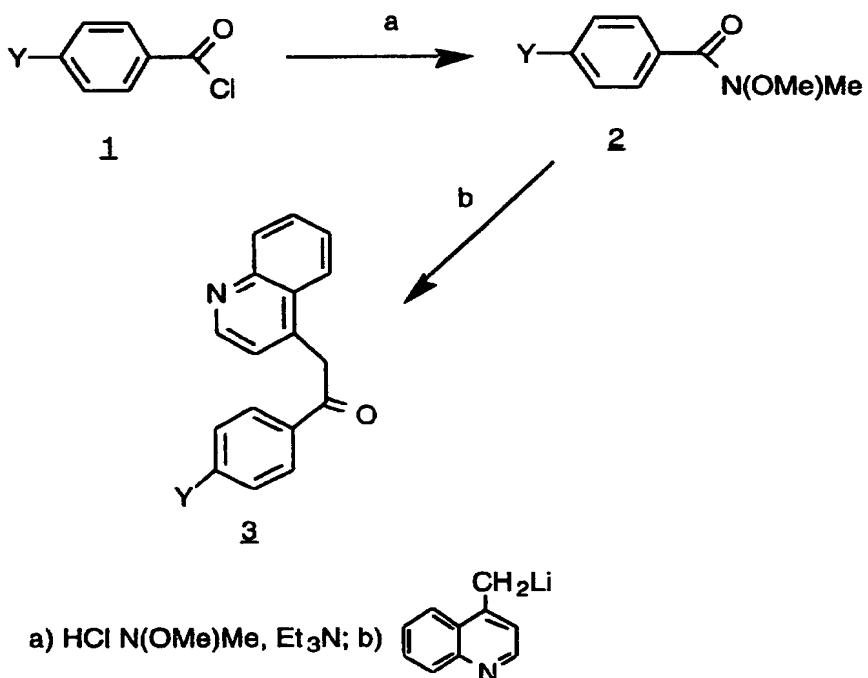


a) $(CH_3O)_2CHN(CH_3)_2$; b) H_2NOH HCl , $EtOH$; c) $NaOH$; d) HCl ; e) $HCONH_2$, NH_3

While the illustration in Schemes V and VI are for the preparation of a particular compound of Formula (III) (i.e., Scheme I, R_1 =-pyridyl, R_2 =4-fluorophenyl, R_4 =amino and R_3 =hydrogen), generalization of the synthesis to groups claimed as R_1 , R_2 and R_3 herein can be achieved by starting with the appropriate acetophenones, preparation of which are disclosed in PCT/US93/00674, notably Scheme VI, whose disclosure is herein incorporated by reference. Conversion to the corresponding enamine 2, isoxazole 3 and propanenitrile 4 is outlined in EP 0 531 901 A2, whose disclosure is incorporated by reference herein. Subsequent treatment of 4 with the appropriately substituted amidine gives a substituted R_3 -4-amino

pyrimidine of Formula (III). Alternatively, appropriately substituted amidines may be used in step (e) to produce directly compounds of Formula (III) which may then be used, as necessary, as intermediates to produce further compounds of Formula (III) through derivatization. Appropriately substituted amidines may be made using the 5 procedures such as those taught in Garigipati, R.S., *Tet. Lett.*, (1990), 31 (14), 1969 whose disclosure is incorporated by reference herein. Pyrimidine 5 can be converted to additional compounds of Formula (III) wherein R4 is the corresponding sulphonamide, amide, urea, guanidine or urethane by using the appropriate acylating agents such as sulfonyl chlorides, isocyanates, dicyanamides and chloroformates, 10 respectively. While it is recognized that in the Scheme I the R4 amino group is unsubstituted, (R5 and R6 = hydrogen) the amino agroup may also be suitably converted to the mono- or di-alkyl derivative by one of skill in the art by appropriate and well known techniques.

15 Scheme VI



The appropriately substituted acetophone, 3-Scheme-6, is prepared by adding the anion of 4-methyl-quinoline (step b), which is prepared by treatment thereof with 20 an alkyl lithium derivative, such as *n*-butyl lithium, to an N-alkyl-O-

alkoxybenzamide. Suitably, the other R₁ moieties may be prepared in an analogous manner. Alternatively, the anion may be condensed with a benzaldehyde, to give an alcohol which is then oxidised to the ketone 3.

5 Suitable protecting groups for use in the present invention, are well known in the art and described in many references, for instance, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981.

Pharmaceutically acid addition salts of compounds of formula (I), (II) or (III) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

10 The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

Synthetic Examples

15 EXAMPLE 1

2-Amino-4-(4-fluorophenyl)-5-(4-pyridyl)pyrimidine

(a) **3-Dimethylamino-1-(4-fluorophenyl)-2-(pyridin-4-yl)-2-propen-1-one** - The title compound was prepared following the procedure of Marusawa, H. *et al.* EP 0 531 901 A2.

20 (b) **2-Amino-4-(4-fluorophenyl)-5-(4-pyridyl)pyrimidine** - The title compound was prepared following the procedure of Bennett, G. *et al.*, *J. Med. Chem.*, 1978, 21(7), 623 except using 3-dimethylamino-1-(4-fluorophenyl)-2-(pyridin-4-yl)-2-propen-1-one: ESMS (*m/z*): 267.0 (M⁺+H).

(c) **2-Acetamido-4-(4-fluorophenyl)-5-(4-pyridyl)pyrimidine**

25 A mixture of 2-amino-4-(4-fluorophenyl)-5-(4-pyridyl)pyrimidine in acetic anhydride is stirred at room temperature. After 72 h the mixture is poured into H₂O and neutralized with conc. NH₄OH. The resulting precipitate is filtered and washed with H₂O. Purification by column chromatography, followed by recrystallization, affords the title compound.

30 EXAMPLE 2

2,4-Diamino-5-(4-fluorophenyl)-6-(4-pyridyl)pyrimidine

(a) **3-Dimethylamino-1-(4-fluorophenyl)-2-(pyridin-4-yl)-2-propene-1-one** - The title compound is prepared following the procedure of Marusawa, H. *et al.* EP 0 531 901 A2.

(b) **5-(4-Fluorophenyl)-4-(pyridin-4-yl)isoxazole** - The title compound is prepared following the procedure of Marusawa, H. *et al.* EP 0 531 901 A2.

(c) **3-(4-Fluorophenyl)-3-oxo-2-(pyridin-4-yl)propanenitrile** - The title compound is prepared following the procedure of Marusawa, H. *et al.* EP 0 531 901 A2.

5 (d) **2,4-Diamino-5-(4-fluorophenyl)-6-(4-pyridyl)pyrimidine** - The title compound is prepared following the procedure of Russell, P.B. *et al.* *J. Amer. Chem. Soc.*, 1951, 73, 3763 except using 3-(4-fluorophenyl)-3-oxo-2-(pyridin-4-yl)propanenitrile.

EXAMPLE 3

10 **4-Amino-6-(4-fluorophenyl)-5-(4-pyridyl)pyrimidine**

(a) **3-Dimethylamino-1-(4-fluorophenyl)-2-(pyridin-4-yl)-2-propen-1-one** - The title compound is prepared following the procedure of Marusawa, H. *et al.* EP 0 531 901 A2.

(b) **5-(4-Fluorophenyl)-4-(pyridin-4-yl)isoxazole** - The title compound is prepared following the procedure of Marusawa, H. *et al.* EP 0 531 901 A2.

15 (c) **3-(4-Fluorophenyl)-3-oxo-2-(pyridin-4-yl)propanenitrile** - The title compound is prepared following the procedure of Marusawa, H. *et al.* EP 0 531 901 A2.

(d) **4-Amino-6-(4-fluorophenyl)-5-(4-pyridyl)pyrimidine** - The title compound is prepared following the procedure of Nagamatsu, T. *et al.* *Synthesis*, 1991, 303 except using 3-(4-fluorophenyl)-3-oxo-2-(pyridin-4-yl)propanenitrile.

20

METHODS OF TREATMENT

The compounds of Formula (I), (II), or (III) or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cell, such as, but not limited to monocytes and/or macrophages.

For simplicity, in the method of treatment section herein, the term "compounds of Formula (I)" should be recognized to mean compounds of Formula (I), (II) or (III).

30 Compounds of formula (I) are capable of inhibiting proinflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF and are therefore of use in therapy. IL-1, IL-8 and TNF affect a wide variety of cells and tissues and these cytokines, as well as other leukocyte-derived cytokines, are important and critical inflammatory mediators of a wide variety of disease states and conditions. The inhibition of these pro-

inflammatory cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

Accordingly, the present invention provides a method of treating a cytokine-mediated disease which comprises administering an effective cytokine-interfering 5 amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In particular, compounds of formula (I) or a pharmaceutically acceptable salt thereof are of use in the prophylaxis or therapy of any disease state in a human, or other mammal, which is exacerbated by or caused by excessive or unregulated IL-1, IL-8 or TNF production by such mammal's cell, such as, but not limited to, monocytes 10 and/or macrophages.

Accordingly, in another aspect, this invention relates to a method of inhibiting the production of IL-1 in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15 There are many disease states in which excessive or unregulated IL-1 production is implicated in exacerbating and/or causing the disease. These include rheumatoid arthritis, osteoarthritis, endotoxemia and/or toxic shock syndrome, other acute or chronic inflammatory disease states such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease, tuberculosis, atherosclerosis, 20 muscle degeneration, multiple sclerosis, cachexia, bone resorption, psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis. Recent evidence also links IL-1 activity to diabetes, pancreatic β cells and Alzheimer's disease.

25 In a further aspect, this invention relates to a method of inhibiting the production of TNF in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof

Excessive or unregulated TNF production has been implicated in mediating or 30 exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, such as osteoporosis, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, 35 such as influenza, cachexia secondary to infection or malignancy, cachexia secondary

to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis.

Compounds of formula (I) are also useful in the treatment of viral infections, 5 where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibiting-compounds of formula (I). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3.

10 Cytomegalovirus (CMV), Influenza, adenovirus and the Herpes group of viruses, such as but not limited to, Herpes Zoster and Herpes Simplex. Accordingly, in a further aspect, this invention relates to a method of treating a mammal, preferably a human, afflicted with a human immunodeficiency virus (HIV) which comprises administering to such mammal an effective TNF inhibiting amount of a compound of formula (I) or a 15 pharmaceutically acceptable salt thereof.

Compounds of formula (I) may also be used in association with the veterinary treatment of mammals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. 20 Examples of such viruses include, but are not limited to, the lentivirus infections such as equine infectious anaemia virus, caprine arthritis virus, visna virus, or the maedi virus, or the retroviruses, such as feline immunodeficiency virus (FIV), bovine immunodeficiency virus, or canine immunodeficiency virus.

The compounds of formula (I) may also be used topically in the treatment or 25 prophylaxis of topical disease states mediated by or exacerbated by excessive cytokine production, such as by IL-1 or TNF respectively, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

30 Another aspect of the present invention relates to a method of inhibiting the production of IL-8 (Interleukin-8, NAP) in a mammal in need thereof which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

35 There are many disease states in which excessive or unregulated IL-8 production is implicated in exacerbating and/or causing the disease. These diseases

are characterized by massive neutrophil infiltration such as, psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. All of these diseases are associated with increased IL-8 production which is responsible for the chemotaxis of neutrophils 5 into the inflammatory site. In contrast to other inflammatory cytokines (IL-1, TNF, and IL-6), IL-8 has the unique property of promoting neutrophil chemotaxis and activation. Therefore, the inhibition of IL-8 production would lead to a direct reduction in the neutrophil infiltration.

The compounds of formula (I) are administered in an amount sufficient to 10 inhibit cytokine, in particular IL-1, IL-8 or TNF, production such that it is regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate or prevent the disease state. Abnormal levels of IL-1, IL-8 or TNF, for instance in the context of the present invention, constitute: (i) levels of free (not cell bound) IL-1, IL- 15 8 or TNF greater than or equal to 1 picogram per ml; (ii) any cell associated IL-1, IL-8 or TNF; or (iii) the presence of IL-1, IL-8 or TNF mRNA above basal levels in cells or tissues in which IL-1, IL-8 or TNF, respectively, is produced.

The discovery that the compounds of formula (I) are inhibitors of cytokines, specifically IL-1, IL-8 and TNF is based upon the effects of the compounds of formulas (I) on the production of the IL-1, IL-8 and TNF in *in vitro* assays which are 20 described herein.

As used herein, the term "inhibiting the production of IL-1 (IL-8 or TNF)" refers to:

- a) a decrease of excessive *in vivo* levels of the cytokine (IL-1, IL-8 or TNF) in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the 25 cytokine by all cells, including but not limited to monocytes or macrophages;
- b) a down regulation, at the genomic level, of excessive *in vivo* levels of the cytokine (IL-1, IL-8 or TNF) in a human to normal or sub-normal levels;
- c) a down regulation, by inhibition of the direct synthesis of the cytokine (IL-1, IL-8 or TNF) as a posttranslational event; or
- 30 d) a down regulation, at the translational level, of excessive *in vivo* levels of the cytokine (IL-1, IL-8 or TNF) in a human to normal or sub-normal levels.

As used herein, the term "TNF mediated disease or disease state" refers to any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 35 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose

production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF.

As used herein, the term "cytokine" refers to any secreted polypeptide that affects the functions of cells and is a molecule which modulates interactions between cells in the immune, inflammatory or hematopoietic response. A cytokine includes, but is not limited to, monokines and lymphokines, regardless of which cells produce them. For instance, a monokine is generally referred to as being produced and secreted by a mononuclear cell, such as a macrophage and/or monocyte. Many other cells however also produce monokines, such as natural killer cells, fibroblasts, basophils, neutrophils, endothelial cells, brain astrocytes, bone marrow stromal cells, epidermal keratinocytes and B-lymphocytes. Lymphokines are generally referred to as being produced by lymphocyte cells. Examples of cytokines include, but are not limited to, Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Tumor Necrosis Factor-alpha (TNF- α) and Tumor Necrosis Factor beta (TNF- β).

As used herein, the term "cytokine interfering" or "cytokine suppressive amount" refers to an effective amount of a compound of formula (I) which will cause a decrease in the *in vivo* levels of the cytokine to normal or sub-normal levels, when given to a patient for the prophylaxis or treatment of a disease state which is exacerbated by, or caused by, excessive or unregulated cytokine production.

As used herein, the cytokine referred to in the phrase "inhibition of a cytokine, for use in the treatment of a HIV-infected human" is a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration.

As TNF- β (also known as lymphotoxin) has close structural homology with TNF- α (also known as cachectin) and since each induces similar biologic responses and binds to the same cellular receptor, both TNF- α and TNF- β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

Compounds of Formula (I) are capable of inhibiting inducible proinflammatory proteins, such as COX-2, also referred to by many other names such as prostaglandin endoperoxide synthase-2 (PGHS-2) and are therefore of use in therapy. These proinflammatory lipid mediators of the cyclooxygenase (CO) pathway are produced by the inducible COX-2 enzyme. Regulation, therefore of COX-2 which is responsible for the these products derived from arachidonic acid, such as

prostaglandins affect a wide variety of cells and tissues are important and critical inflammatory mediators of a wide variety of disease states and conditions.

Expression of COX-1 is not effected by compounds of Formula (I). This selective inhibition of COX-2 may alleviate or spare ulcerogenic liability associated with

5 inhibition of COX-1 thereby inhibiting prostoglandins essential for cytoprotective effects. Thus inhibition of these pro-inflammatory mediators is of benefit in controlling, reducing and alleviating many of these disease states. Most notably these inflammatory mediators, in particular prostaglandins, have been implicated in pain, such as in the sensitization of pain receptors, or edema. This aspect of pain

10 management therefore includes treatment of neuromuscular pain, headache, cancer pain, and arthritis pain. Compounds of Formula (I) or a pharmaceutically acceptable salt thereof, are of use in the prophylaxis or therapy in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

Accordingly, the present invention provides a method of inhibiting the

15 synthesis of COX-2 which comprises administering an effective amount of a compound of Formula (I), (II), or (III) or a pharmaceutically acceptable salt thereof. The present invention also provides for a method of prophylaxis treatment in a human, or other mammal, by inhibition of the synthesis of the COX-2 enzyme.

A new member of the MAP kinase family, alternatively termed CSBP, p38,

20 or RK, has been identified independently by several laboratories recently. Activation of this novel protein kinase via dual phosphorylation has been observed in different cell systems upon stimulation by a wide spectrum of stimuli, such as physicochemical stress and treatment with lipopolysaccharide or proinflammatory cytokines such as interleukin-1 and tumor necrosis factor. The cytokine biosynthesis inhibitors of the

25 present invention may be determined to be potent and selective inhibitors of CSBP/p38/RK kinase activity by the assay as described herein. These inhibitors are of aid in determining the signaling pathways involvement in inflammatory responses. In particular, for the first time a definitive signal transduction pathway can be prescribed to the action of lipopolysaccharide in cytokine production in

30 macrophages. In addition to those diseases already noted, treatment of stroke, neurotrauma, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes and pancreatic β cells, multiple sclerosis, muscle degeneration, eczema, psoriasis, sunburn, and conjunctivitis are also included.

The cytokine inhibitors were subsequently tested in a number of animal models for anti-inflammatory activity. Model systems were chosen that were relatively insensitive to cyclooxygenase inhibitors in order to reveal the unique activities of cytokine suppressive agents. The inhibitors exhibited significant activity

5 in many such in vivo studies. Most notable are its effectiveness in the collagen-induced arthritis model and inhibition of TNF production in the endotoxic shock model. In the latter study, the reduction in plasma level of TNF correlated with survival and protection from endotoxic shock related mortality. Also of great importance are the compounds effectiveness in inhibiting bone resorption in a rat

10 fetal long bone organ culture system. Griswold et al., (1988) *Arthritis Rheum.* 31:1406-1412; Badger, et al., (1989) *Circ. Shock* 27, 51-61; Votta et al., (1994) *in vitro. Bone* 15, 533-538; Lee et al., (1993). *B Ann. N. Y. Acad. Sci.* 696, 149-170.

In order to use a compound of formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of formula (I), pharmaceutically acceptable salts thereof and pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of formula (I) may be administered in conventional dosage forms prepared by combining a compound of formula (I) with standard pharmaceutical carriers according to conventional procedures. The compounds of formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid

carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

5 A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid

10 suspension.

15 Compounds of formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of formula (I) externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous,

20 intraperitoneal and intramuscular administration.

25 Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

30 25 Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

35 30 Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard,

soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent

5 such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily

10 solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100° C. for half an hour.

15 Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

20 Compounds of formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such administration may be prepared by conventional techniques. Compounds of formula

25 (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

For all methods of use disclosed herein for the compounds of formula (I), the daily oral dosage regimen will preferably be from about 0.1 to about 80 mg/kg of total

30 body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5 mg to 15mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily.

35 The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to

about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the 5 particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment 10 determination tests.

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

15 **BIOLOGICAL EXAMPLES**

The cytokine-inhibiting effects of compounds of the present invention are determined by the following *in vitro* assays:

Interleukin 1 (IL-1)

Human peripheral blood monocytes are isolated and purified from either fresh 20 blood preparations from volunteer donors, or from blood bank buffy coats, according to the procedure of Colotta *et al.*, J Immunol, 132, 936 (1984). These monocytes (1×10^6) are plated in 24-well plates at a concentration of 1-2 million/ml per well. The cells are allowed to adhere for 2 hours, after which time non-adherent cells are removed by gentle washing. Test compounds are then added to the cells for 1h before 25 the addition of lipopolysaccharide (50 ng/ml), and the cultures are incubated at 37°C for an additional 24h. At the end of this period, culture super-natants are removed and clarified of cells and all debris. Culture supernatants are then immediately assayed for IL-1 biological activity, either by the method of Simon *et al.*, J. Immunol. Methods, 84, 85, (1985) (based on ability of IL-1 to stimulate a Interleukin 2 30 producing cell line (EL-4) to secrete IL-2, in concert with A23187 ionophore) or the method of Lee *et al.*, J. ImmunoTherapy, 6 (1), 1-12 (1990) (ELISA assay).

Tumor Necrosis Factor (TNF)

Human peripheral blood monocytes are isolated and purified from either blood bank buffy coats or plateletpheresis residues, according to the procedure of Colotta, R. *et al.*, *J Immunol*, **132**(2), 936 (1984). The monocytes are plated at a density of 5 1×10^6 cells/ml medium/well in 24-well multi-dishes. The cells are allowed to adhere for 1 hour after which time the supernatant is aspirated and fresh medium (1ml, RPMI-1640, Whitaker Biomedical Products, Whitaker, CA) containing 1% fetal calf serum plus penicillin and streptomycin (10 units/ml) added. The cells are incubated for 45 minutes in the presence or absence of a test compound at 1nM-10mM dose 10 ranges (compounds were solubilized in dimethyl sulfoxide/ethanol, such that the final solvent concentration in the culture medium is 0.5% dimethyl sulfoxide/0.5% ethanol). Bacterial lipopoly-saccharide (*E. coli* 055:B5 [LPS] from Sigma Chemicals Co.) is then added (100 ng/ml in 10 ml phosphate buffered saline) and cultures incubated for 15 16-18 hours at 37°C in a 5% CO₂ incubator. At the end of the incubation period, culture supernatants are removed from the cells, centrifuged at 3000 rpm to remove 20 cell debris. The supernatant is then assayed for TNF activity using either a radio-immuno or an ELISA assay, as described in WO 92/10190 and by Becker *et al.*, *J Immunol*, 1991, **147**, 4307.

20 In vivo TNF assay:

While the above indicated assay is an in vitro assay, the compounds of Formula (I), (II) or (III) may also be tested in an in vivo system such as described in :

- (1) "Differentiation *In Vivo* of Classical Non-Steroidal Antiinflammatory Drugs from Cytokine Suppressive Antiinflammatory Drugs and Other 25 Pharmacological Classes Using Mouse Tumour Necrosis Factor Alpha Production", Griswold *et al.*, Drugs Under Exp. and Clinical Res., **XIX** (6), 243-248 (1993); or in
- (2) Boehm, *et al.*, 1-substituted 4-aryl-5-pyridinylimidazoles - a new class of cytokine 30 suppressive drugs with low 5-lipoxygenase and cyclooxygenase inhibitory potency. *Journal Of Medicinal Chemistry* 39, 3929-3937 (1996) whose disclosures are incorporated by reference herein in their entirety.

The IL-8 cytokine-inhibiting effects of compounds of the present invention may be determined by the following *in vitro* assay.

Receptor Binding Assays:

35 [¹²⁵I] IL-8 (human recombinant) is obtained from Amersham Corp., Arlington Heights, IL, with specific activity 2000 Ci/mmol. All other chemicals are of analytical

grade. High levels of recombinant human IL-8 type α and β receptors are individually expressed in Chinese hamster ovary cells as described previously (Holmes, *et al.*, *Science*, 1991, 253, 1278). The Chinese hamster ovary membranes are homogenized according to a previously described protocol (Haour, *et al.*, *J Biol Chem.*, 249 pp 5 2195-2205 (1974)). Except that the homogenization buffer is changed to 10mM Tris-HCl, 1mM MgSO₄, 0.5mM EDTA (ethylene-diaminetetra-acetic acid), 1mMPMSF (α -toluenesulphonyl fluoride), 0.5 mg/L Leupeptin, pH 7.5. Membrane protein concentration is determined using Pierce Co. micro-assay kit using bovine serum albumin as a standard. All assays are performed in a 96-well micro plate format.

10 Each reaction mixture contains ¹²⁵I IL-8 (0.25 nM), 0.5 μ g/mL of IL-8Ra or 1.0 μ g/mL of IL-8Rb membranes in 20 mM Bis-Trispropane and 0.4 mM Tris HCl buffers, pH 8.0, containing 1.2 mM MgSO₄, 0.1 mM EDTA, 25 mM NaCl and 0.03% CHAPS. In addition, the drug or compound of interest is added which has been pre-dissolved in DMSO so as to reach a final concentration of between 0.01nM and 100 15 μ M. The assay is initiated by addition of ¹²⁵I-IL-8. After 1 hour at room temperature the plate is harvested using a Tomtec 96-well harvester onto a glass fiber filtermat blocked with 1% polyethylenimine/0.5% BSA and washed 3 times with 25 mM NaCl, 10 mM TrisHCl, 1 mM MgSO₄, 0.5 mM EDTA, 0.03 % CHAPS, pH 7.4. The filter is then dried and counted on the Betaplate liquid scintillation counter. The 20 recombinant IL-8 R α , or Type I, receptor is also referred to herein as the non-permissive receptor and the recombinant IL-8 R β , or Type II, receptor is referred to as the permissive receptor.

Cytokine Specific Binding Protein Assay

25 A radiocompetitive binding assay was developed to provide a highly reproducible primary screen for structure-activity studies. This assay provides many advantages over the conventional bioassays which utilize freshly isolated human monocytes as a source of cytokines and ELISA assays to quantify them. Besides being a much more facile assay, the binding assay has been extensively validated to 30 highly correlate with the results of the bioassay. A specific and reproducible cytokine inhibitor binding assay was developed using soluble cytosolic fraction from THP.1 cells and a radiolabeled compound. Patent Application USSN 08/123175 Lee *et al.*, filed September 1993, Lee *et al.*, PCT 94/10529 filed 16 September 1994 and Lee *et al.*, *Nature* 300, n(72), 739-746 (Dec. 1994) whose disclosures are incorporated by 35 reference herein in its entirety describes the above noted method for screening drugs

to identify compounds which interact with and bind to the cytokine specific binding protein (hereinafter CSBP). However, for purposes herein the binding protein may be in isolated form in solution, or in immobilized form, or may be genetically engineered to be expressed on the surface of recombinant host cells such as in phage 5 display system or as fusion proteins. Alternatively, whole cells or cytosolic fractions comprising the CSBP may be employed in the screening protocol. Regardless of the form of the binding protein, a plurality of compounds are contacted with the binding protein under conditions sufficient to form a compound/ binding protein complex and compound capable of forming, enhancing or interfering with said complexes are 10 detected.

CSBP KINASE ASSAY:

This assay measures the CSBP-catalyzed transfer of ^{32}P from [α - ^{32}P]ATP to threonine residue in an epidermal growth factor receptor (EGFR)-derived peptide 15 (T669) with the following sequence: KRELVEPL~~T~~PSGEAPNQALLR (residues 661- 681). (See Gallagher et al., "Regulation of Stress Induced Cytokine Production by Pyridinyl Imidazoles: Inhibition of CSBP Kinase", BioOrganic & Medicinal Chemistry, to be published 1996).

Kinase reactions (total volume 30 μl) contain: 25 mM Hepes buffer, pH 7.5; 20 10 mM MgCl_2 ; 170 μM ATP⁽¹⁾; 10 μM Na ortho vanadate; 0.4 mM T669 peptide; and 20-80 ng of yeast-expressed purified CSBP2 (see Lee et al., *Nature* 300, n(72), 739-746 (Dec. 1994)). Compounds (5 μl from [6X] stock⁽²⁾) are pre-incubated with the enzyme and peptide for 20 min on ice prior to starting the reactions with 25 $^{32}\text{P}/\text{MgATP}$. Reactions are incubated at 30 °C for 10 min and stopped by adding 10 μl of 0.3 M phosphoric acid. ^{32}P -labeled peptide is separated on phosphocellulose (Wattman, p81) filters by spotting 30 μl reaction mixture. Filters are washed 3 times with 75 mM phosphoric acid followed by 2 washes with H_2O , and counted for ^{32}P .

(1) The K_m of CSBP for ATP was determined to be 170 μM . Therefore, compounds screened at the K_m value of ATP.

30 (2) Compounds are usually dissolved in DMSO and are diluted in 25 mM Hepes buffer to get final concentration of DMSO of 0.17%.

Prostaglandin endoperoxide synthase-2 (PGHS-2) assay:

The following assay describes a method for determining the inhibitory effects of compounds of Formula (I) on human PGHS-2 protein expression in LPS stimulated human monocytes.

5 **Method:** Human peripheral blood monocytes were isolated from buffy coats by centrifugation through Ficoll and Percoll gradients. Cells were seeded at 2 X 10⁶/well in 24 well plates and allowed to adhere for 1 hour in RPMI supplemented with 1% human AB serum, 20mM L-glutamine, Penicillin-Streptomycin and 10mM HEPES. Compounds were added at various concentrations and incubated at 37°C 10 for 10 minutes. LPS was added at 50 ng/well (to induce enzyme expression) and incubated overnight at 37°C. The supernatant was removed and cells washed once in cold PBS. The cells were lysed in 100μl of cold lysis buffer(50mM Tris/HCl pH 7.5, 150mM NaCl, 1% NP40, 0.5% sodium deoxycholate, 0.1% SDS, 300ug/ml 15 DNase, 0.1% TRITON X-100, 1mM PMSF, 1mM leupeptin, 1mM pepstatin). The lysate was centrifuged (10,000 X g for 10 min. at 4°C) to remove debris and the soluble fraction was subjected to SDS PAGE. analysis (12% gel). Protein separated on the gel were transferred onto nitrocellulose membrane by electrophoretic means for 2 hours at 60 volts. The membrane was pretreated for one hour in PBS/0.1% Tween 20 with 5% non-fat dry milk. After washing 3 times in PBS/Tween buffer, 20 the membrane was incubated with a 1:2000 dilution of a monospecific antiserum to PGHS-2 or a 1:1000 dilution of an antiserum to PGHs-1 in PBS/Tween with 1% BSA for one hour with continuous shaking. The membrane was washed 3X in PBS/Tween and then incubated with a 1:3000 dilution of horseradish peroxidase conjugated donkey antiserum to rabbit Ig (Amersham) in PBS/Tween with 1% BSA 25 for one hour with continuous shaking. The membrane was then washed 3X in PBS/Tween and the ECL immunodetection system (Amersham) was used to detect the level of expression of prostaglandin endoperoxide synthases-2.

30 **Results:** The following compounds were tested and found to be active in this assay (i.e., inhibited LPS induced PGHS-2 protein expression in rank order potency similar to that for inhibiting cytokine production as noted in assays indicated): 4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)imidazole; 6-(4-Fluorophenyl)-2,3-dihydro-5-(4-pyridinyl)imidazo[2,1-b]thiazole; and Dexamethasone

Several compounds were tested and found to be inactive (up to 10uM):

2-(4-Methylsulfinylphenyl)-3-(4-pyridyl)-6,7-dihydro-(5H)-pyrrolo[1,2-a]imidazolerolipram ; phenidone and NDGA. None of the compounds tested was found to inhibit PGHS-1 or cPLA₂ protein levels in similar experiments.

5 TNF- α in Traumatic Brain Injury Assay

The present assay provides for examination of the expression of tumor necrosis factor mRNA in specific brain regions which follow experimentally induced lateral fluid-percussion traumatic brain injury (TBI) in rats. Adult Sprague-Dawley rats (n=42) are anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to 10 lateral fluid-percussion brain injury of moderate severity (2.4 atm.) centered over the left temporaparietal cortex (n=18), or "sham" treatment (anesthesia and surgery without injury, n=18). Animals are sacrificed by decapitation at 1, 6 and 24 hr. post injury, brains removed, and tissue samples of left (injured) parietal cortex (LC), corresponding area in the contralateral right cortex (RC), cortex adjacent to injured 15 parietal cortex (LA), corresponding adjacent area in the right cortex (RA), left hippocampus (LH) and right hippocampus (RH) are prepared. Total RNA is isolated and Northern blot hybridization is performed and quantitated relative to an TNF- α positive control RNA (macrophage = 100%). A marked increase of TNF- α mRNA expression is observed in LH (104 \pm 17% of positive control, p < 0.05 compared with 20 sham), LC (105 \pm 21%, p < 0.05) and LA (69 \pm 8%, p < 0.01) in the traumatized hemisphere 1 hr. following injury. An increased TNF- α mRNA expression is also observed in LH (46 \pm 8%, p < 0.05), LC (30 \pm 3%, p < 0.01) and LA (32 \pm 3%, p < 0.01) at 6 hr. which resolves by 24 hr. following injury. In the contralateral hemisphere, 25 expression of TNF- α mRNA is increased in RH (46 \pm 2%, p < 0.01), RC (4 \pm 3%) and RA (22 \pm 8%) at 1 hr. and in RH (28 \pm 11%), RC (7 \pm 5%) and RA (26 \pm 6%, p < 0.05) at 6 hr. but not at 24 hr. following injury. In sham (surgery without injury) or naive animals, no consistent changes in expression of TNF- α mRNA is observed in any of the 6 brain areas in either hemisphere at any times. These results indicate that 30 following parasagittal fluid-percussion brain injury, the temporal expression of TNF- α mRNA is altered in specific brain regions, including those of the non-traumatized hemisphere. Since TNF- α is able to induce nerve growth factor (NGF) and stimulate the release of other cytokines from activated astrocytes, this post-traumatic alteration in gene expression of TNF- α plays an important role in both the acute and regenerative response to CNS trauma.

CNS Injury model for IL- β mRNA

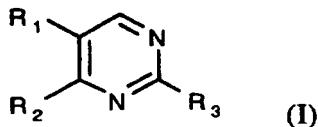
This assay characterizes the regional expression of interleukin-1 β (IL-1 β) mRNA in specific brain regions following experimental lateral fluid-percussion traumatic brain injury (TBI) in rats. Adult Sprague-Dawley rats (n=42) are 5 anesthetized with sodium pentobarbital (60 mg/kg, i.p.) and subjected to lateral fluid-percussion brain injury of moderate severity (2.4 atm.) centered over the left temporoparietal cortex (n=18), or "sham" treatment (anesthesia and surgery without injury). Animals are sacrificed at 1, 6 and 24 hr. post injury, brains removed, and tissue samples of left (injured) parietal cortex (LC), corresponding area in the 10 contralateral right cortex (RC), cortex adjacent to injured parietal cortex (LA), corresponding adjacent area in the right cortex (RA), left hippocampus (LH) and right hippocampus (RH) were prepared. Total RNA is isolated and Northern blot hybridization is performed and the quantity of brain tissue IL-1 β mRNA is presented as percent relative radioactivity of IL-1 β positive macrophage RNA which is loaded 15 on same gel. At 1 hr. following brain injury, a marked and significant increase in expression of IL-1 β mRNA is observed in LC (20.0 \pm 0.7% of positive control, n=6, p < 0.05 compared with sham animal), LH (24.5 \pm 0.9%, p < 0.05) and LA (21.5 \pm 3.1%, p < 0.05) in the injured hemisphere, which remained elevated up to 6 hr. post injury in the LC (4.0 \pm 0.4%, n=6, p < 0.05) and LH (5.0 \pm 1.3%, p < 0.05). 20 In sham or naive animals, no expression of IL-1 β mRNA is observed in any of the respective brain areas. These results indicate that following TBI, the temporal expression of IL-1 β mRNA is regionally stimulated in specific brain regions. These regional changes in cytokines, such as IL-1 β play a role in the post-traumatic pathologic or regenerative sequelae of brain injury.

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The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, 30 utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound of the formula:



5 wherein:

wherein:

R₁ is 4-pyridyl, 4-pyrimidinyl, 4-quinazolinyl, 4-quinolyl, or 6-isoquinoliny, which rings are optionally substituted with one or two substituents, each of which is independently selected from Y, NHR_a, optionally substituted C₁₋₄ alkyl, halogen, hydroxyl, optionally substituted C₁₋₄ alkoxy, optionally substituted C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl substituted amino, or N(R₁₀)C(O)R_b;

Y is X₁-R_a;

X₁ is oxygen or sulfur;

15 R_a is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl, heteroaryl, heteroarylC₁₋₆alkyl, wherein each of these moieties may be optionally substituted;

R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl, wherein each of these moieties may be optionally substituted;

20 R₂ is an optionally substituted aryl or optionally substituted heteroaryl group, provided that both R₁ and R₂ are not the same heteroaryl group;

and when R₂ is an optionally substituted aryl ring, the ring is substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano, -C(Z)NR₁₃R₁₄, -C(Z)OR₂₃, -(CR₁₀R₂₀)_nCOR₃₆, -SR₁₅, -SOR₁₅, -OR₃₆, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, -ZC(Z)R₃₆, -NR₁₀C(Z)R₂₃, or -(CR₁₀R₂₀)_nNR₁₀R₂₀ and which, for other positions of substitution, is halo, cyano, -C(Z)NR₁₆R₂₆, -C(Z)OR₈, -(CR₁₀R₂₀)_nCOR₈, -S(O)_mR₈, -OR₈, halo-substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, -(CR₁₀R₂₀)_nNR₁₀C(Z)R₈, -NHS(O)_mR₇, -NHS(O)_mNR₁₃R₁₄, -NR₇S(O)_mR₇, -NR₇S(O)_mNR₁₃R₁₄ wherein m' is 1 or 2, -ZC(Z)R₈ or -(CR₁₀R₂₀)_nNR₁₆R₂₆;

30 and when R₂ is an optionally substituted heteroaryl group, the substituent groups include one or two substituents each of which is independently selected

from C₁-4 alkyl, halo, C₁-4 alkoxy, C₁-4 alkylthio, NR₁₀R₂₀, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂;

m is 0 or an integer of 1 or 2;

5 n is 0 or an integer of 1 or 2;

R₃ is hydrogen, NR₅R₆, NHS(O)₂R₇, NR₁₀C(Z)R₈, NR₁₀C(Z)NR₅R₆, NR₁₀C(=NR₁₁)NR₅R₆, or NR₁₀C(Z)OR₁₀; wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl moieties of R₇, and R₈ may be optionally substituted;

10 R₅ and R₆ are each independently selected from hydrogen or optionally substituted C₁-4 alkyl, optionally substituted aryl or optionally substituted aryl-C₁-4 alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉;

15 Z is oxygen or sulfur;

R₇ is C₁-10 alkyl, C₃-7 cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁-10alkyl, heteroaryl or heteroarylalkyl;

R₈ is hydrogen, C₁-10 alkyl, C₃-7 cycloalkyl, heterocyclyl, heterocyclyl C₁-10alkyl, aryl, arylC₁-10 alkyl, heteroaryl or heteroarylC₁-10 alkyl;

20 R₉ is hydrogen, -C(Z)R₈ or optionally substituted C₁-10 alkyl, S(O)₂R₇, optionally substituted aryl or optionally substituted aryl-C₁-4 alkyl;

R₁₀ and R₂₀ is each independently selected from hydrogen or C₁-6 alkyl;

R₁₁ is hydrogen, cyano, C₁-4 alkyl, C₃-7 cycloalkyl or aryl;

R₁₂ is R₁₀ or C(Z)-C₁-4 alkyl, optionally substituted aryl, optionally substituted arylC₁-4 alkyl, or S(O)₂R₇;

25 R₁₃ and R₁₄ is each independently selected from hydrogen or C₁-4 alkyl or R₁₃ and R₁₄ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₂₂;

30 R₁₅ is hydrogen, C₁-4 alkyl, C₂-4 alkenyl, C₂-4 alkynyl or NR₁₃R₁₄, provided that the moiety -SR₁₅ is not -SNR₁₃R₁₄ and the moiety -S(O)R₁₅ is not -SOH;

R₁₆ and R₂₆ is each independently selected from hydrogen or optionally substituted C₁-4 alkyl, optionally substituted aryl or optionally substituted aryl-C₁-4 alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to

7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂ ;

R₂₂ is R₁₀ or C(Z)-C₁₋₄ alkyl;

R₂₃ is C₁₋₄ alkyl, halo-substituted-C₁₋₄ alkyl, or C₃₋₅ cycloalkyl;

5 R₃₆ is hydrogen or R₂₃;
or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 wherein R₁ is an optionally substituted 4-pyridyl or 4-pyrimidinyl.

10 3. The compound according to Claim 1 wherein R₂ is an optionally substituted phenyl.

4. The compound according to Claim 3 wherein the one or more optional 15 substituents are independently selected from halogen or methoxy.

5 The compound according to Claim 1 wherein R₃ is NR₅R₆, NHS(O)₂R₇, NR₁₀C(Z)R₈, or NR₁₀C(Z)NR₅R₆.

20 6. The compound according to Claim 5 wherein R₅ and R₆ are hydrogen or optionally substituted C₁₋₄ alkyl.

7. A pharmaceutical composition comprising a compound according to Claim 1 and one or more pharmaceutically acceptable carriers or diluents.

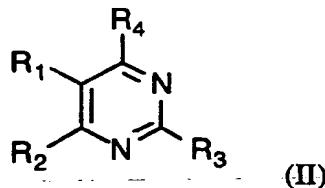
25 8. A method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to Claim 1.

30 9. The method according to Claim 8 wherein the mammal is afflicted with a CSBP/RK/p38 kinase mediated disease which is psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory

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distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple 5 sclerosis, muscle degeneration, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

10. A compound of the formula:



10 wherein:

R₁ is 4-pyridyl, 4-pyrimidinyl, 4-quinazolinyl, 4-quinolyl, or 6-isoquinoliny, which rings are optionally substituted with one or two substituents, each of which is independently selected from Y, NHR_a, optionally substituted C₁₋₄ alkyl, halogen, hydroxyl, optionally substituted C₁₋₄ alkoxy, optionally substituted C₁₋₄ alkylthio, C₁₋₄ alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁₋₆ alkyl 15 substituted amino, or N(R₁₀)C(O)R_b;

Y is X₁-R_a;

X₁ is oxygen or sulfur;

R_a is C₁₋₆alkyl, aryl, arylC₁₋₆alkyl, heterocyclic, heterocyclylC₁₋₆ alkyl, 20 heteroaryl, heteroarylC₁₋₆alkyl, wherein each of these moieties may be optionally substituted;

R_b is hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, aryl, arylC₁₋₄ alkyl, heteroaryl, heteroarylC₁₋₄alkyl, heterocyclyl, or heterocyclylC₁₋₄ alkyl, wherein each of these 25 moieties may be optionally substituted;

R₂ is an optionally substituted aryl or optionally substituted heteroaryl group, provided that both R₁ and R₂ are not the same heteroaryl group; wherein when one R₂ is an optionally substituted aryl ring, the ring is substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano, -C(Z)NR₁₃R₁₄, 30 -C(Z)OR₂₃, -(CR₁₀R₂₀)_n COR₃₆, -SR₁₅, -S(O)R₁₅, -OR₃₆, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, -ZC(Z)R₃₆, -NR₁₀C(Z)R₂₃, or -(CR₁₀R₂₀)_n NR₁₀R₂₀ and which, for other positions of substitution, is halo, cyano, -C(Z)NR₁₆R₂₆.

-C(Z)OR₈, -(CR₁₀R₂₀)_nCOR₈, -S(O)_mR₈, -OR₈, halo-substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, -(CR₁₀R₂₀)_nNR₁₀C(Z)R₈, -NHS(O)_mR₇, -NHS(O)_mNR₁₃R₁₄, -NR₇S(O)_mR₇, -NR₇S(O)_{m'}NR₁₃R₁₄ wherein m' is 1 or 2, -ZC(Z)R₈ or -(CR₁₀R₂₀)_nNR₁₆R₂₆; and when R₂ is an optionally substituted heteroaryl group, the substituent groups include one or two substituents each of which is independently selected from C₁₋₄ alkyl, halo, C₁₋₄ alkoxy, C₁₋₄ alkylthio, NR₁₀R₂₀, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂;

5 m is 0 or an integer of 1 or 2;

n is 0 or an integer of 1 or 2;

R₃ and R₄ are independently NR₅R₆, NHS(O)₂R₇, NR₁₀C(Z)R₈, NR₁₀C(Z)NR₅R₆, NR₁₀C(=NR₁₁)NR₅R₆, or NR₁₀C(Z)OR₁₀;

R₅ and R₆ are each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉;

10 Z is oxygen or sulfur;

15 R₇ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroarylalkyl; wherein all of these moieties may be optionally substituted;

20 R₈ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl; wherein all of these moieties may be optionally substituted;

25 R₉ is hydrogen, -C(Z)R₈ or optionally substituted C₁₋₁₀ alkyl, S(O)₂R₇, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl;

R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl;

R₁₁ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;

30 R₁₂ is R₁₀ or C(Z)-C₁₋₄ alkyl;

R₁₃ and R₁₄ is each independently selected from hydrogen or C₁₋₄ alkyl or R₁₃ and R₁₄ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₇;

R15 is hydrogen, C₁-4 alkyl, C₂-4 alkenyl, C₂-4 alkynyl or NR₁₃R₁₄, provided that the moiety -SR₁₅ is not -SNR₁₃R₁₄ and the moiety -S(O)R₁₅ is not -SOH;

R₁₆ and R₂₆ is each independently selected from hydrogen or optionally substituted C₁-4 alkyl, optionally substituted aryl or optionally substituted aryl-C₁-4 alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₉;

5 R₁₇ is hydrogen of C(Z)-C₁-4 alkyl;

R₂₃ is C₁-4 alkyl, halo-substituted-C₁-4 alkyl, or C₃-5 cycloalkyl;

10 R₃₆ is hydrogen or R₂₃;
or a pharmaceutically acceptable salt thereof.

11. The compound according to Claim 10 wherein R₁ is an optionally substituted 4-pyridyl or 4-pyrimidinyl.

15 12. The compound according to Claim 10 wherein R₂ is an optionally substituted phenyl.

13. The compound according to Claim 12 wherein the one or more optional 20 substituents are independently selected from halogen or methoxy.

14. The compound according to Claim 10 wherein R₃ and R₄ are independently NR₅R₆.

25 15. The compound according to Claim 14 wherein R₅ and R₆ are independently hydrogen or optionally substituted C₁-4 alkyl.

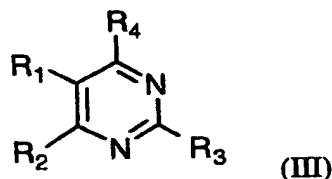
16. A pharmaceutical composition comprising a compound according to Claim 10 and one or more pharmaceutically acceptable carriers or diluents.

30 17. A method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to Claim 10.

18. The method according to Claim 17 wherein the mammal is afflicted with a CSBP/RK/p38 kinase mediated disease which is psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other 5 arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerulonephritis, diabetes, graft vs. host reaction, 10 allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

19. A compound of the formula:

15



wherein:

R₁ is 4-pyridyl, 4-pyrimidinyl, 4-quinazolinyl, 4-quinolyl, or 6-isoquinolinyl, which 20 rings are optionally substituted with one or two substituents, each of which is independently selected from Y, NHR_a, optionally substituted C₁-4 alkyl, halogen, hydroxyl, optionally substituted C₁-4 alkoxy, optionally substituted C₁-4 alkylthio, C₁-4 alkylsulfinyl, CH₂OR₁₂, amino, mono and di- C₁-6 alkyl substituted amino, or N(R₁₀)C(O)R_b;

Y is X₁-R_a;

25 X₁ is oxygen or sulfur;

R_a is C₁-6alkyl, aryl, arylC₁-6alkyl, heterocyclic, heterocyclylC₁-6 alkyl, heteroaryl, heteroarylC₁-6alkyl, wherein each of these moieties may be optionally substituted;

30 R_b is hydrogen, C₁-6 alkyl, C₃-7 cycloalkyl, aryl, arylC₁-4 alkyl, heteroaryl, heteroarylC₁-4alkyl, heterocyclyl, or heterocyclylC₁-4 alkyl, wherein each of these moieties may be optionally substituted;

R₂ is an optionally substituted aryl or optionally substituted heteroaryl group, provided that both R₁ and R₂ are not the same heteroaryl group; wherein when

one R₂ is an optionally substituted aryl ring, the ring is substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is halo, cyano, -C(Z)NR₁₃R₁₄, -C(Z)OR₂₃, -(CR₁₀R₂₀)_n COR₃₆, -SR₁₅, -S(O)R₁₅, -OR₃₆, halo-substituted-C₁₋₄ alkyl, C₁₋₄ alkyl, -ZC(Z)R₃₆, -NR₁₀C(Z)R₂₃, or -(CR₁₀R₂₀)_n NR₁₀R₂₀ and which, for other positions of substitution, is halo, cyano, -C(Z)NR₁₆R₂₆, -C(Z)OR₈, -(CR₁₀R₂₀)_n COR₈, -S(O)_mR₈, -OR₈, halo-substituted-C₁₋₄ alkyl, -C₁₋₄ alkyl, -(CR₁₀R₂₀)_n NR₁₀C(Z)R₈, -NHS(O)_mR₇, -NHS(O)_mNR₁₃R₁₄, -NR₇S(O)_mR₇, -NR₇S(O)_m'NR₁₃R₁₄, -ZC(Z)R₈ or -(CR₁₀R₂₀)_n NR₁₆R₂₆;

and when R₂ is an optionally substituted heteroaryl group, the substituent groups include one or two substituents each of which is independently selected from C₁₋₄ alkyl, halo, C₁₋₄ alkoxy, C₁₋₄ alkylthio, NR₁₀R₂₀, or an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₂;

15 m is 0 or an integer of 1 or 2;
 m' is an integer of 1 or 2;
 m" is an integer having a value of 1 to 10;
 n is 0 or an integer of 1 or 2;
 n' is 0 or an integer having a value of 1 to 10;

20 n" is an integer having a value of 1 to 10
 R₃ is hydrogen, C₁₋₁₀ alkyl, halosubstituted C₁₋₁₀ alkyl, -(CR₁₀R₂₀)_{n'} Q-(Y₁)_t, -(CR₁₀R₂₀)_{n'}(Y₂)_p, -(CR₁₀R₂₀)_{n''}(Y₃)_p, or -(CR₁₀R₂₀)_{m''}(Y₄)_p;
 p is 0 or an integer of 1 or 2;
 t is an integer of 1, 2, or 3;

25 Q is an aryl or heteroaryl group;
 Y₁ is independently selected from hydrogen, halogen, C₁₋₅ alkyl, halo-substituted C₁₋₅ alkyl, -(CR₁₀R₂₀)_{n'}(Y₂)_p, -(CR₁₀R₂₀)_{n''}(Y₃)_p, or -(CR₁₀R₂₀)_{m''}(Y₄)_p;
 Y₂ is halogen, -OR₈, -S(O)_mR₁₈, -SR₈, -S(O)_{m'}OR₈, -S(O)_mNR₈R₉, or -O(CR₁₀R₂₀)_nNR₈R₉, -ZC(O)R₈, or -OC(Z)NR₈R₉;

30 Y₃ is -NR₈R₉, -NR₁₀C(Z)R₈, -NR₁₀C(Z)NR₈R₉, -NR₁₀S(O)_mR₁₈, -N(OR₂₁)C(Z)NR₈R₉, -N(OR₂₁)C(Z)R₈, -NR₁₀C(=NR₁₁)SR₁₈, -NR₁₀C(=NR₁₁)NR₈R₉, -NR₁₀C(=CR₁₄R₂₄)SR₁₈, -NR₁₀C(=C(R₂₄)₂)NR₈R₉, -NR₁₀C(O)C(O)NR₈R₉, -NR₁₀C(O)C(O)OR₁₀, -NR₁₀S(O)_mCF₃, or -NR₁₀C(Z)OR₁₀;

Y₄ is -C(O)R₈, -CO₂R₈, -CO₂(CR₁₀R₂₀)_m CONR₈R₉, -CN, -C(Z)NR₈R₉, -C(Z)NR₈OR₉, -C(=NOR₂₁)R₈, -C(=NR₁₉)NR₈R₉, -C(=NOR₁₉)NR₈R₉, -C(=NR₁₉)ZR₁₈, -NR₁₀S(O)_mCF₃, or -NR₁₀C(Z)OR₁₀;

R₄ is hydrogen, NR₅R₆, NHS(O)₂R₇, NR₁₀C(Z)R₈, NR₁₀C(Z)NR₅R₆.

5 NR₁₀C(=NR₁₁)NR₅R₆, or NR₁₀C(Z)OR₁₀; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl, heterocyclic and heterocyclic alkyl moieties of R₇, and R₈ may be optionally substituted;

10 R₅ and R₆ are each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₇;

Z is oxygen or sulfur;

R₇ is C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, aryl, arylalkyl, heterocyclyl,

15 heterocyclyl-C₁₋₁₀alkyl, heteroaryl or heteroarylalkyl;

R₈ is hydrogen, C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, heterocyclyl, heterocyclyl C₁₋₁₀alkyl, aryl, arylC₁₋₁₀ alkyl, heteroaryl or heteroarylC₁₋₁₀ alkyl;

R₉ is hydrogen, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl or R₈ and R₉ may

20 together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₁₇;

R₁₀ and R₂₀ is each independently selected from hydrogen or C₁₋₄ alkyl;

R₁₁ is hydrogen, cyano, C₁₋₄ alkyl, C₃₋₇ cycloalkyl or aryl;

25 R₁₂ is R₁₀ or C(Z)-C₁₋₄ alkyl;

R₁₃ and R₁₄ is each independently selected from hydrogen or C₁₋₄ alkyl or R₁₃ and R₁₄ together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR₂₂;

30 R₁₅ is hydrogen, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl or NR₁₃R₁₄, provided that the moiety -SR₁₅ is not -SNR₁₃R₁₄ and the moiety -S(O)R₁₅ is not -SOH;

R₁₆ and R₂₆ is each independently selected from hydrogen or optionally substituted C₁₋₄ alkyl, optionally substituted aryl or optionally substituted aryl-C₁₋₄ alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of 5 to

7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR17;

R17 is hydrogen, -C(Z)R8 or optionally substituted C1-10 alkyl, S(O)2R7, optionally substituted aryl or optionally substituted aryl-C1-4 alkyl;

5 R18 is C1-10 alkyl, halo-substituted C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C3-7 cycloalkyl, C5-7 cycloalkenyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R19 is hydrogen, C1-10 alkyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;

R21 is hydrogen, a pharmaceutically acceptable cation, C1-10 alkyl, C3-7 cycloalkyl,

10 aryl, aryl C1-4 alkyl, heteroaryl, heteroarylalkyl, heterocyclyl, aroyl, or C1-10 alkanoyl;

R22 is R10 or C(Z)-C1-4 alkyl;

R23 is C1-4 alkyl, halo-substituted-C1-4 alkyl, or C3-5 cycloalkyl;

R24 is independently selected from hydrogen, alkyl, nitro or cyano;

15 R36 is hydrogen or R23;

or a pharmaceutically acceptable salt thereof.

20. The compound according to Claim 19 wherein R1 is an optionally substituted 4-pyridyl or 4-pyrimidinyl.

20. The compound according to Claim 19 wherein R2 is an optionally substituted phenyl.

22. The compound according to Claim 21 wherein the one or more optional

25 substituents are independently selected from halogen or methoxy.

23. The compound according to Claim 19 wherein R4 is NR5R6, NHS(O)2R7, NR10C(Z)R8, or NR10C(Z)NR5R6.

30 24. The compound according to Claim 23 wherein R5 and R6 are hydrogen or optionally substituted C1-4 alkyl.

25. The compound according to Claim 19 wherein R3 is hydrogen, -(CR10R20)_n'Q-(Y1)_t, -(CR10R20)_n'(Y2)_p, -(CR10R20)_n"(Y3)_p, or -(CR10R20)_m"(Y4)_p; Q is an aryl; and t is 1.

26. A pharmaceutical composition comprising a compound according to Claim 19 and one or more pharmaceutically acceptable carriers or diluents.
27. A method of treating a CSBP/RK/p38 kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to Claim 19.
28. The method according to Claim 27 wherein the mammal is afflicted with a CSBP/RK/p38 kinase mediated disease which is psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerularnephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease, Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermititis, psoriasis, sunburn, or conjunctivitis.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04121

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C07D 401/04; A61K 31/505

US CL : 514/256, 275; 544/324, 328, 331

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/256, 275; 544/324, 328, 331

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online Structure Search - files Registry, CAPLus, Beilstein, Marpat, WPIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	US 5,507,974 A (GOMPPER ET AL.) 16 April 1996 (16/04/96).	1-7, 10-16, 19-26
A	US 4,504,482 A (LESHER ET AL.) 12 March 1985 (12/03/95).	1-28
A	Chem. abstr., Vol.121, No.15, 10 October 1994 (Columbus, OH, USA), page 1076, column 1, the abstract No. 179540t, MOEHRLE et al., 'Reactions of CH-activated pyridyl derivatives with 1,3,5-triazine.' Arch. Pharm. 1994, 8(327), 533-534, (Ger).	1-7, 10-16, 19-26

 Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

03 JUNE 1997

Date of mailing of the international search report

24 JUN 1997

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/04121

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chem, abstr., Vol.101, No.25, 17 December 1984 (Columbus. OH, USA), page 756, column 1-column 2, the abstract No. 230461j, HUNG et al., 'Investigations into the synthesis of 6-ethyl-5-(4-pyridinyl)-2,4-pyrimidinediamine as a potential antimarial agent.' Journal of Heterocyclic Chemistry. 1984, 21(3), 741-744 (Eng).	1-28